

**GENETICS FOR
MEDICAL STUDENTS**

GENETICS FOR MEDICAL STUDENTS

by

E B FORD

M.A. D.Sc., F.R.S.

Reader in Genetics in the University of Oxford

WITH 10 DIAGRAMS

THIRD EDITION



METHUEN & CO LTD LONDON
36 Essex Street, Strand, W C 2

TO
PROFESSOR W H LE GROS CLARK FRS

First Published	July 26th 1948
Second Edition, Revised	May 1948
Third Edition	1948

CATALOGUE NO. 8301/U
PRINTED IN GREAT BRITAIN

PREFACE

THE IMPORTANCE of Genetics is being widely recognised by the Medical Profession. Practitioners require a knowledge of this subject in the course of their work, and students are faced with it in examinations. Yet though text-books of Genetics are available in great variety the number of them which treat of human heredity is small. Indeed a work providing a brief and elementary introduction to that subject has long been required, and this book is an attempt to meet that need.

The scope of this account has to some extent been determined by the experience gained during many years of teaching Genetics to medical students at Oxford. I have made no attempt to present a compendium of knowledge on the subject. On the contrary the book is designed to illustrate its chief principles. Consequently the various inherited conditions which are described have been chosen as illustrative instances only. However a classified list of some of the more important, or well authenticated, of the genes known in Man is provided on pp. 149-51. Further information on them should be obtained from works devoted to special branches of human Genetics. Among these, one is of such outstanding merit that I wish to draw attention to it here: I refer to E. A. Cockayne's *Inherited Abnormalities of the Skin and its Appendages* (Oxford Press, 1933).

The examples which I have employed are mainly human, but I have made sparing use of other material where this seemed particularly appropriate and helpful. Thus to describe autosomal linkage without reference to lower forms would greatly embarrass the explanation of a phenomenon which has an important bearing on medical work.

I hope that those who read this book will not be content to end their genetic studies with it. In a brief Bibliography I have suggested a few works which supply more detailed information on the subjects covered by each chapter so that students may be able to extend their knowledge in the

a source of constant encouragement and help in all branches of my work.

It is very important that a discussion of human Genetics should conform to the requirements of the medical profession; nor is its precise scope, judged from that point of view easy to define. I have been particularly fortunate, therefore, in obtaining the advice of Professor W. R. Le Gros Clark, F.R.S., upon this matter. Indeed, it was at his suggestion that this book was written. It is a pleasure to record my gratitude to him for the very considerable trouble which he has taken in reading and criticising it. I should also like to express my grateful thanks to Professor E. S. Goodrich, F.R.S., for his help. Professor G. D. Hale Carpenter has been so kind as to read the proofs, and his comments have been of great assistance to me.

Dr G. L. Taylor of the Galton Laboratory Serum Unit, has given me the benefit of his valuable advice on those sections of this book which deal with blood-grouping. I am most grateful for his help. I am indebted to the Editor of the *Annals of Eugenics* for permission to publish Fig. 9 and Table F. I should like to express my thanks to Mrs. M. Nicholson for the care which she has taken in preparing Figs. 1-8.

It had been my intention to submit each chapter of this book, as it was written, to my cousin, William Howland Thurnam, M.D., the well-known authority on tuberculosis. The keen interest which he took in its plan was an incentive to write it. His death during the course of the work has been a great loss to me. The advice of one who was eminent not only in the medical profession but as a literary critic and artist of exceptional attainments, would have been of much value in preparing this survey of human Genetics.

E. B. F

OXFORD,

February 1942

PREFACE TO THE SECOND EDITION

A SECOND EDITION of this book is required in little more than two years since its first publication, and in that time the subject has not advanced sufficiently to necessitate considerable alterations except in regard to the Rh blood group. The recent work in this field is of much importance since it provides a basis for the treatment of a rather common condition of the new-born. As accounts of it are not yet available in text books, Messrs. Methuen & Co. have kindly allowed me to add a third Appendix (page 152) in which I have summarized the subject. I have, in addition, introduced a few other recent results, and made a number of corrections elsewhere in the text. I am much indebted to Professor I. Munro Fox, F.R.S. for most kindly drawing my attention to two paragraphs which required adjustment, and to Professor W. E. Le Gros Clark, F.R.S., for his valuable help.

CONTENTS

	PAGE
PREFACE	1
CHAPTER	
I. MENDELIAN HEREDITY	v
I. Mendel's Two Laws. II. Linkage and Crossing over. III. Multiple Allelomorphs	
II. THE GENETICS OF SEX	23
I. Sex-determination. II. Sex-linkage—(a) Total Sex-linkage in the X-chromosome—(b) Partial Sex-linkage—() Total Sex-linkage in the Y-chromosome. III. The Sex-ratio	
III. MUTATION AND THE NATURE OF HEREDITY	37
I. Mutation. II. The Nature of Heredity	
IV. THE ACTION OF THE GENES	74
I. The Effects of the Genes. II. Dominance Modification. III. Environmental Variation. IV. Genetic Physiology in Man	
V. POLYMORPHISM	99
I. Introduction. II. The Taste Test. III. The Blood-groups—() The O, A, B Series—(b) The M, N Series—(c) The RH Group. IV. Practical Applications	
VI. METHODS OF STUDY IN HUMAN GENETICS	119
I. Elementary Quantitative Methods. II. Linkage in Man. III. The Detection of Inherited Conditions. IV. Eugenics	

GENETICS FOR MEDICAL STUDENTS

APPENDIX—L Cytology	141
II Classified List of Some Human Genes	149
III The Rh Group	152
BIBLIOGRAPHY	153
REFERENCES	153
INDEX	159

CHAPTER I

MENDELIAN HEREDITY

I. MENDEL'S TWO LAWS

THE HUMAN BODY with all its attributes, is a product of heredity and environment. Neither of these two agencies is constant, and changes in them may lead to variations in one or more physical or mental characters. In studying the interaction of two variables it is always desirable to consider each separately before examining their joint effects. Therefore we will first discuss the operation of inheritance, and subsequently analyse the part played by the environment and its interaction with heredity (see Chapter IV).

The characters of the body in the widest sense, are controlled by hereditary factors (or *genes*) present in every cell. They are passed from parent to offspring in the gametes. These genes exist in pairs, called 'allelomorphs' whose members are derived the one from the father and the other from the mother. The two genes composing such allelomorphic pairs may either be similar ('homosygous') or dissimilar ('heterosygous'), and the individuals possessing such allelomorphs are called 'homosygotes' and 'heterosygotes' respectively. The simplest situation therefore is that in which a given character is determined by a pair of hereditary factors. Instead of contaminating each other when brought together into the same cell ('blending inheritance' pp. 68-9), the genes retain their identity ('particulate inheritance', pp. 68-70); even the unlike members of a pair of heterosygous allelomorphs remain quite distinct. Fertilization is an additive process; for the gametes are effectively only half a cell each, and they combine to produce the 'zygote' which is the first cell of the new organism. Some mechanism must therefore exist by which the members of each allelomorphic pair of genes are separated from one another and pass into

Those who have no knowledge of Cytology are recommended to read Appendix I (pp. 141-8) before beginning this book.

different gametes. These then contain but one member of each of the allelomorphs, the pairs being restored at fertilization.

These conclusions on the nature of heredity were first enunciated by Father Gregor Mendel (1822-84), working at the Augustinian monastery of St. Thomas at Brno (then called Brünn) in Moravia, of which he lived to become Pralat. He summarized his results in the form of two laws. The first of these may now be considered.

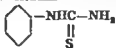
Mendel's First Law (The Law of Segregation) states that characters are controlled by pairs of genes the members of which separate, or *segregate*, from one another during the formation of the germ-cells and pass into different gametes. The pairs are restored at fertilization, which allows of their recombination in definite proportions. Consequently the characters to which they give rise may also segregate: for they will appear in subsequent generations with definite numerical frequencies.

It will be apparent that this law is concerned with two sets of events. The behaviour of the genes, and that of the characters to which they give rise. Segregation relates fundamentally to the separation of the pairs of genes from one another and their passage into different gametes, but it was inferred from the visible separation, or segregation, of the characters which those genes control. A mating between two organisms which differ from one another in respect of a pair of contrasted characters (p. 58) produces a heterozygous form whose appearance, for our immediate purpose, is immaterial. Mendel found that if two such heterozygotes are crossed, the original types will emerge from the hybrid mixture as pure as they were before: that is, they segregate in the succeeding generation, and in definite proportions.

When Mendel published his results in 1866, no mechanism was known which could effect the segregation of the genes. However his work was long ignored and only received due attention in 1900 sixteen years after his death. By that time the chromosomes had been discovered, and it was soon

obvious that these constitute vehicles perfectly adapted to carry the genes and to ensure their segregation. The parallel is indeed striking between the behaviour of the chromosomes, detected by the microscopic study of cells, and that of the genes, determined by tracing the inheritance of the characters which they control. The genes are present in pairs (allelomorphs) as are the chromosomes (homologous chromosomes). The members of these pairs, both of genes and of chromosomes, are derived respectively from the two parents. Consequent upon Mendelian segregation, the genes constituting the allelomorphs separate from one another and pass into different gametes, as do the members of the homologous pairs of chromosomes, owing to meiosis. The gametes then contain one member only of the pairs both of genes and of chromosomes; but these are restored by the additive nature of fertilisation. It will later become apparent that other equally exact parallels exist between chromosomes and genes (for example, those provided by crossing-over' pp 145-6.) But the chromosome theory of heredity is not dependent upon mere similarity of behaviour however striking; that the chromosomes carry the genes is a fact which has now been demonstrated by many critical experiments.

It will at this stage be helpful to take an example of the working of Mendel's first law. Several other consequences of its operation can then easily be appreciated. For this purpose we will trace the inheritance of a peculiar condition of no direct, though of considerable indirect, importance (p. 108). In mankind, about one individual in four is unable to taste the organic compound phenyl-thio-urea and some of its chemical allies in concentrations so low as fifty parts per million.¹ This substance is intensely bitter to those who can detect it, and has the formula:



For survey of this subject, see Elliott and Dean (1909), or Waddington (1930).

¹Non-tasters' can often detect it in concentrations of 400 parts per million (in aqueous solution).

The ability to taste it is due to the action of a pair of genes, which may be denoted TT . However they may exist in another form (tt) responsible for the inability to do so. These two types are both homozygous, for the allelomorphs with which we are concerned are made up of similar members both T or both t . They are carried respectively on a pair of homologous chromosomes which separate from each other during meiosis, one member passing into each gamete. This brings about segregation, so that every gamete contains one member only of the genes determining the power to taste phenyl thio-urea. Thus a 'taster' produces gametes each containing a single T while those of a 'non-taster' each contain t only. Should a taster and a non-taster marry their children will possess pairs of homologous chromosomes once more, whose components are derived from the father and from the mother. These will each carry a gene controlling this particular tasting faculty. Thus the pairs of allelomorphs are restored, but these are heterozygous pairs (Tt), composed of T from one parent and t from the other (Fig 1).

In some conditions the operation of two unlike allelomorphs gives rise to an intermediate effect (p. 118). More often, however the heterozygotes closely or completely resemble one of the homozygous types. In these circumstances, when the same result is produced in the heterozygote as in one of the homozygotes, the character is called a dominant. The alternative character which is obscured in the heterozygote and appears only in the other homozygote, is called a recessive. The inability to taste phenyl-thio-urea is recessive, so that the heterozygotes manifest the dominant condition and are tasters.

Heterozygous individuals, produced by a mating of two homozygotes, are said to constitute the 'first filial (or F_1)' generation of the family which is being investigated. The original parents then belong to the 'first parental (P_1)' generation. When it is necessary to refer to the grandparents of the F_1 generation, these are denoted by P_2 and so on backwards. A mating between two individuals of the F_1 generation gives rise to a 'second filial (F_2)' generation.

This cannot normally be studied directly in man, since it arises from a brother and sister marriage. However its equivalent, for our present purpose, is constantly encountered, a marriage between two heterozygotes. The results to which this gives rise must be considered in some detail.

A heterozygous taster carries the dissimilar allelomorphs *Tt*. Consequent upon meiosis (see Appendix I), the gametes

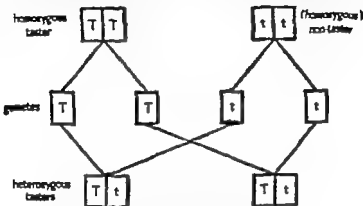


Fig. 1. The production of heterozygotes from marriage between the two contrasted heterozygous types. The characters are the ability to taste phenyl-thio-carb, which is dominant to the inability to do so.

receive one member only of this pair of genes, *T* or *t*. Sperms or eggs carrying one type or the other are thus produced in equality. On a marriage between two such heterozygotes, the chances are equal that a sperm carrying *T* meets an egg carrying *T* or *t*, so producing zygotes of the constitution *TT* and *Tt* in equal numbers. Similarly with the equally numerous sperms carrying *t* which, meeting the two types of eggs as before, produce *Tt* and *tt* zygotes, also in equal numbers. Three types of offspring therefore arise, possessing *TT*, *Tt*, and *tt*, in a ratio of 1 : 2 : 1. These are the proportions always produced from the random combination of two types having equally numerous alternative phases: they are

not the prerogative of genetics. If we toss together two coins a considerable number of times, our throws give 25 per cent both obverse; 50 per cent, one obverse and one reverse; and 25 per cent both reverse; three groups in a ratio of 1 : 2 : 1 as in the genetic instance. However in the example which we are studying the three classes of zygote constituting the F_2 generation will not give rise to three distinct classes of individuals: tasters, imperfect tasters, and non tasters, for as already mentioned, the first two of these are combined due to dominance. Consequently two classes only appear: tasters and non-tasters, in a 3 : 1 ratio, representing a 1 : 2 : 1 ratio with the first two terms added together (Fig. 2).

In discussing the P_1 generation of this example no indication was given whether the taster was the male or the female parent, and none is needed. Save for those instances especially related to the sex-determination mechanism, to be discussed in Chapter II, the two sexes are exactly equal in the contribution which they make to the heredity of the offspring, and the result is the same however the genotypes or the characters are distributed in regard to sex. It will now be evident, moreover, that dominants can be of two genetic types, homozygotes or heterozygotes, while recessives can be of one type only for they must always be homozygous.

We have just examined the result of a marriage between two heterozygotes. It is now necessary to consider the highly important situation in which one parent is a heterozygote and the other a homozygote. For this purpose we will use the same character as before, the ability or inability to taste phenyl thio-urea.

As already indicated, a heterozygous taster bears the genes Tt on a homologous pair of chromosomes, and these separate during meiosis, carrying T into one half of the gametes and t into the other. However the non-taster being recessive can only be homozygous, and possess tt ; that is, all the gametes which they form are similar and carry t . In a marriage involving these two types it is immaterial which of them is the male and which the female, and it

chances are equal that the gametes of the non-tasters, necessarily provided with t , meet gametes bearing T or t produced by the heterozygote. Thus when the pairs of homologous chromosomes, and consequently the allelomorphs, are restored at fertilization, the combinations Tt (tasters) and tt

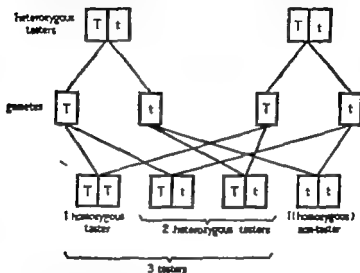


Fig. 2. Segregation among the children of marriage between two heterozygotes. The characters are the same as in Fig. 1.

(non-tasters) are produced in equality: heterozygotes and homozygotes appear in a ratio of 1 : 1. This simple type of mating is called a 'back-cross' because it results when a heterozygote, of the F_1 generation, is crossed back to one of the parental forms: but it must not be so defined, for it can arise in other ways. Rather the following definition should be employed. A back-cross is a mating between a heterozygote and a homozygote, and it leads to segregation in equality. This expresses all the essential features of the

situation. The individuals produced by a back-cross constitute what is called an R_2 generation (Fig. 8).

With an intermediate heterozygote, a back-cross to either homozygote will lead to the segregation of distinct characters. When dominance is complete, however, this result is attained only by the back-cross to the recessive. That to the homozygous dominant produces an apparently uniform R_2 ,

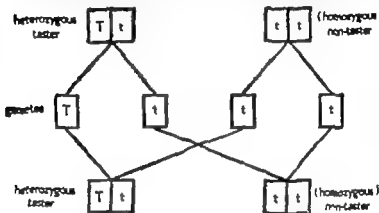


Fig. 8. A back-cross (heterozygote \times homozygote), showing that segregation takes place in a ratio of 1:1 among the offspring of this type of marriage. The characters are the same as in Figs. 1 and 2.

resembling both parents, but consisting of homozygotes and heterozygotes in equality. The reality of this segregation, concealed as it is, could be established if the members of such a R_2 generation were to mate with recessive individuals. Half of them would then produce the dominant type only and half would produce dominants and recessives in equality.

The class of test just suggested is an important one. For if we wish to determine the genetic constitution of an individual during experimental work on animals and plants, it is always desirable to cross it with the recessive type. The advantage of this is evident, since recessives are of known constitution, being necessarily homozygous, and allow the

demonstrable segregation of recessives as well as dominants among their offspring when mated with heterozygotes. A test of this kind can, of course, be employed to prove the truth of an assertion made at an earlier stage that the 3:1 ratio obtained in F_2 segregation is, in reality a ratio of 1:2:1 obscured by dominance. If such segregating dominants be mated with recessives, one third of them will produce dominants only. The remaining two thirds will produce dominants and recessives in equality: this is a back cross result, and it arises from matings between recessives and the concealed heterozygotes. Clearly the dominant class of the F_2 generation is a composite one, including homozygotes and heterozygotes in a ratio of 1:2, as postulated on theoretical grounds.

We have now considered the two types of segregation which can take place with single-factor inheritance: that characteristic of the F_2 generation and of the back-cross. Furthermore, we have seen that it is possible to demonstrate the occurrence in both of them of the fundamental ratios expected, even when these are obscured by dominance. It has already been stressed that one of the most important properties of such segregation is the reappearance of the original homozygous types among the offspring of heterozygotes. When a marriage occurs between two similar homozygotes, both non-tasters or both homozygous tasters in our example, all the progeny are homozygotes also. Further the type remains pure indefinitely until a mating with the heterozygote or with the other homozygote takes place. That is to say a homozygous line always breeds true, whether the genes have passed through a heterozygote or not, and unlike genes do not contaminate one another even when brought together into the same cell. Thus Mendelian heredity has provided an entirely new concept of the hybrid, one of mosaic not of blended type, and of the purity of the hereditary units.

Both the ability and the inability to taste phenyl-thio-urea are very common conditions in the population. However the study of hereditary disease constitutes an important

aspect of human genetics, and here one of the alternative states will be rare. This leads to certain situations which require brief mention.

Friedreich's Ataxia is a rare disorder in which a degeneration of the nervous system produces at first a loss of power in the lower extremities. The patient sways as he stands, and walks with difficulty. Later the ataxia involves the trunk, arms, and head, speech becomes difficult, and advanced cases may be unable to sit up. The condition is inherited as a simple recessive and, consequently it can hardly ever arise except from a mating between two heterozygotes. Since the disease usually appears during the second decade of life, those affected by it will certainly reproduce less frequently than normal individuals. Even so, all their offspring will almost invariably be of the normal (dominant) type; for only when they marry a close relative (pp. 184-5) is there any reasonable possibility of a back-cross result, which would show that the ostensibly healthy partner in the union is in reality a heterozygote. Still less is it likely that a marriage between two affected persons will ever be observed. Thus it is clear that those suffering from a rare disease inherited as a simple recessive will almost always have normal parents and, at first sight, the condition will appear merely sporadically in the history of affected families.

Special qualifications are also necessary in considering rare conditions inherited as simple dominants. All affected individuals will then have an affected parent: a direct history of the condition being traceable in one ancestral line in unbroken succession (except for the rare occurrence of mutation, see Chapter III). Consequently the gene concerned is perpetuated through a series of back-crosses, producing normal and affected heterozygous individuals in approximate equality in each generation. Matings between two heterozygotes, each therefore manifesting the rare disease in question, are liable to be of immense rarity. They are most likely to arise from the marriage of close relations and in those conditions in which the disability does not appear until after the normal age of parenthood. Huntington's Chorea

is a simple dominant of this kind, though so far studied only in the heterozygous phase, for the symptoms seldom become noticeable before the age of thirty and often later. It is characterized by involuntary muscular movements, and mental deterioration progressing to insanity.

It will be clear that the circumstances attending the transmission of a rare dominant disease hardly ever permit its manifestation in the homozygous form. Now the definition of a dominant condition is one in which the effect of the heterozygote is indistinguishable from that of one of the homozygotes. Yet in the vast majority of the rare characters which have been described as simple dominants in man, no opportunity has arisen for comparing them in these phases. Here dominance in reality means no more than that the disease, or other characteristic in question, is unifactorial and is expressed in the heterozygotes. In other animals and plants, in which experimental studies are usually possible, such a situation should not be described as a dominant until the heterozygotes have been compared with both homozygotes and found to agree with one of them. For the occurrence of true dominance is of much evolutionary significance (Chapter IV) and should not be confused with that in which the heterozygous effect is separately detectable. In man, however, it may be extremely difficult or impossible to obtain the information necessary to draw this distinction, while the term dominance has been so widely applied that it might hardly be practicable to attempt severely to limit its use. However, it should always be clearly indicated whether or not the nature of dominant characters has been established. Indeed, it is highly probable that many of those that are so called in man are not, strictly speaking, dominants at all (pp. 85-6).

The analysis so far undertaken has related to the segregation of a single pair of allelomorphs upon the basis of the first law of Mendel. His second law is concerned with the behaviour of two or more pairs of genes when studied together.

Mendel's Second Law (The Law of Independent Assortment)

states: When two or more pairs of genes segregate simultaneously the distribution of any one of them is independent of the distribution of the others.

That is to say if we consider two characters segregating in a 3:1 ratio, this law tells us that nothing interferes with the random distribution of each, there is no tendency for the parental combinations to be preserved in the offspring nor for the two dominant and the two recessive types to segregate together. Rather the result will be the mathematical combination of two 3:1 ratios; that is to say a ratio of 9:3:3:1.

It is now known that Mendel's second law is subject to exceptions (pp. 23-9). However its simple operation must be discussed before these are considered, and this may be done most conveniently with the help of an example.

We will take for this purpose the character already used for illustrating Mendel's first law the ability to taste phenyl thio-urea, which is dominant to the inability to do so, and consider its segregation in relation to that of another character the possession of bright red hair which is unifactorial and recessive to non-red shades. Actually the existence of a small amount of red pigment in the hair sometimes associated with freckles, may represent the heterozygous condition. If so, such heterozygous expression is rather variable and not always achieved, nor is it fully proved. However the point is not one which need concern us.

The full red haired condition, being recessive, must be homozygous, and is due to the operation of a pair of genes which may be denoted *rr*. The dominant non-red haired state being represented as *RR* or *Rr*. Attention should be directed to this nomenclature. It is a convention to employ the same letter for allelomorphous genes, using the capital for that producing dominant effects and the small letter for that producing recessive ones. The initial letter of one of the characters is selected when appropriate. By this means the relation between allelomorphs is apparent when symbols alone are employed.

The double homozygous dominant (*TTRR*) is a taster

with non-red hair. Men and women of this kind produce gametes possessing one member of each allelomorphic pair. They must therefore be all alike, carrying both T and R . Similarly the double recessive ($ttrr$), which is a non-taster with red hair, produces gametes all equipped with t and r . On a marriage between such individuals (the P_1 generation) an F_1 generation is produced which must consist of a single type: double heterozygotes of the constitution $TtRr$ and these, manifesting the two dominant states, will be tasters with non-red hair.

Consider a marriage in which the partners are similar to this F_1 generation. Both will carry T and t respectively upon one pair of homologous chromosomes, and R and r upon another pair in every cell of the body. During meiosis the pairs of chromosomes will separate from one another into different gametes at random, in the sense that there is no tendency for the paternally and maternally derived material of each pair the sections containing the spindle attachment, for example, to pass into the same gametes together. Consequently the chances are equal that T becomes included in a gamete with R or with r similarly for the equally numerous t genes. Thus four kinds of gametes, carrying TR , Tt , tR , and tr are formed in equal numbers by each individual.

These gametic types can be combined in sixteen possible ways, illustrated in Fig. 4. But they give rise only to four distinct classes, owing to dominance. It will be observed that nine of the recombinations contain at least one dominant member of both pairs of allelomorphs, and so are tasters with non-red hair: three possess RR and at least one R and are non-tasters with non-red hair: three possess rr and at least one T being tasters and red haired, while one is of the double recessive type $ttrr$ a non-taster with red hair. These four groups arise in a ratio 9 : 3 : 3 : 1 which represents their frequency in such a F_2 generation.

Only one true-breeding member of each of the four classes is included in a family of this kind ($TTRR$, $ttrr$, TTr and ttr). Consequently the proportion of homozygotes becomes progressively less in the larger of them. An inspection of

		F ₁ gametes			
		TR	Tr	tR	tr
F ₁ gametes	TR	TTRR taster non red hair	TTRr taster non-red hair	TtRR taster non-red hair	TtRr taster non-red hair
	Tr	TTRr taster non-red hair	TTrr taster red hair	TtRr taster non-red hair	Ttrr taste red hair
	tR	TtRR taste non-red hair	TtRr taster non-red hair	ttRR non-taster non red hair	ttRr non-taster non-red hair
	tr	TtRr taster non-red hair	Ttrr taster red hair	ttRr non taster non-red hair	ttrr non-taster red hair

Fig. 4. Segregation among the offspring of two double heterozygotes. The characters are the ability to taste phenyl-thio-urea, dominant to the inability to do so, and the possession of non-red hair which is dominant to the red-haired condition. Each heterozygote manifests the two dominant types, and carries *T* and *t* in one homologous pair of chromosomes and *R* and *r* in another. They therefore produce four classes of gametes in equality. These can be combined in 16 possible ways, producing a generation composed of: 9 tasters with non-red hair 3 tasters with red hair 3 non-tasters with non-red hair and 1 non-taster with red hair.

Fig. 4 also shows the form of segregation which would have taken place in the absence of dominance. All the genetically distinct classes would then have been separable. There are nine of these,¹ segregating in a ratio of 1 : 2 : 2 : 4 : 2 : 2 : 1 : 1.

They are *TTRR*, *TTrr*, *TtRR*, *TtRr*, *TtRr*, *ttRR*, *Ttrr*, *ttRr*, *ttrr*.

It is important to examine the situation arising from a back-cross involving two independently assorting allelomorphs. We have seen that the double heterozygote ($TtRr$) being a taster with non-red hair must produce four types of gametes (TR , Tr , tR , tr) in equal numbers (p. 10). Also that the non-tasters with red hair who are double recessives ($ttrr$), can produce one type only (tr). Clearly a marriage between two such individuals must yield all four classes of offspring, tasters with non-red hair and with red hair non-tasters with non-red and with red hair. Since this is a back-cross, constituting an R_2 generation, these will segregate in equality (pp. 13-14). This result is illustrated in the lowest horizontal line of Fig. 4.

We have now analysed the working of Mendel's second law in both of the fundamental genetic situations: those provided by the F_2 generation and the back-cross. For this purpose we used the simplest instance, that in which two pairs of allelomorphs only are segregating. However this second law indicates the ratios to be expected when three or higher numbers of allelomorphs are involved. Thus the 'tri-hybrid' ratio, that arising from a union in which both parents are heterozygous for three pairs of allelomorphs, leads, with dominance, to the combination of three $3:1$ ratios independently; that is to say to a ratio of $27:9:9:9:8:8:8:1$. There are now twenty-seven genetically distinct classes and, without dominance, each of these would produce a separate effect. A mating between the triple heterozygote, manifesting all three dominant characters, and the triple recessive will yield eight classes. These will appear in equality for this is a back-cross in respect of all three factors.

In conclusion, it must be noticed that the operation of Mendel's second law provides an opportunity for genes which have arisen separately to be brought together. This is obviously of great value, since it allows advantageous characters possessed by different stocks or races to be combined in the same individual.

II. LINKAGE AND CROSSING-OVER

As already explained, it is now established that the genes are carried in the chromosomes (p. 9). This fact sets a limit to the operation of truly independent assortment, so that Mendel's second law is not invariably applicable.

The number of allelomorphs possessed by the human species is of course unknown. General considerations, depending on the possible size of the molecules constituting the genes, suggest that the total must amount to many thousands. There are twenty four pairs of chromosomes in man, so it is obvious that each of them must carry a large number of genes. These cannot assort independently as Mendel thought they did, since they travel in the same vehicle and consequently may be expected to reach the same destination. There is, of course, no barrier to the independent assortment of allelomorphs carried in different pairs of chromosomes, and this is the situation which we have so far analysed. It is indeed that generally to be anticipated in the study of a few sets of allelomorphs only for the human chromosomes do not differ considerably from one another in size, so that the chances are not likely to be much greater than 1 in 24 that any two pairs of allelomorphs are carried together in one of them. Exceptions to Mendel's second law of the kind just indicated, constitute linkage. This should be defined in the following terms:

Linkage is the tendency for two or more pairs of allelomorphs to assort together instead of obeying Mendel's second law of independent assortment, because they are carried in the same pair of chromosomes.

It will be convenient at the outset to illustrate linkage by means of a purely hypothetical example. Consider two heterozygous allelomorphs Aa and Bb which are carried in the same pair of chromosomes. We will first suppose that A and B lie together in one homologous pair of chromosomes and a and b in the other. Consequently the genetic constitution of such a 'dihybrid' individual may be represented

AB/ab .¹ It may be regarded as the F1 generation of a cross whose parents, of the P1 generation, we shall study subsequently. At meiosis the homologous chromosome pairs separate, carrying $AB/$ together into one half of the gametes and $ab/$ together into the other half. Now double recessive individuals (ab/ab) can give rise to one kind of gamete only bearing $ab/$. On a mating between these two types, a back cross generation is produced consisting of two classes only AB/ab and ab/ab instead of the four classes which should arise with independent assortment (compare the example of this on p. 20).

Suppose the genes had been differently arranged in the double heterozygote, A and b being carried on one chromosome and a and B on the other to give the constitution Ab/aB . On mating with the double recessive (ab/ab), which produces $ab/$ gametes only two classes instead of the expected four will again arise; but this time they are Ab/ab and aB/ab .

These facts require brief consideration. In the first instance, the genes A and B were carried together in one chromosome of the double heterozygote and a and b were carried in the other. That is to say the two dominants were linked in one chromosome and the two recessives in the other. On crossing with the double recessive, that same association is preserved, for only the double dominant and double recessive types appear. In the second instance, one dominant and one recessive were carried together in each homologous chromosome. This condition was preserved also in the segregating back-cross family which contains two classes of individuals only possessing one dominant and one recessive character each. The situation presented by the first example, in which the double dominants and double recessives remain together is called *Coupling*. That in which

Cross within the same chromosome will be represented together on one side of the line, thus $AB/$. This represents the condition when no homologous partner exists, as in the gametes, the other side of the line being thus blank. When both homologous chromosomes are present, the line will separate the allelomorphs carried respectively in them, thus AB/ab . I owe this excellent notation to Professor H. A. Fisher.

one dominant character does not appear in the same individual as the other so that dominants and recessives seem to be repelled from one another is called *Repulsion*. It is represented by the second instance.

Yet the parents of the coupling and of the repulsion phase were exactly the same in appearance. The double recessive was of identical constitution in each, and may therefore be disregarded. The double heterozygotes would manifest the two dominant conditions in both examples, though the distribution of the genes was different in them. Their homologous chromosomes contained A and B a and b in coupling, but A and b a and B in repulsion. This is due to the fact that these double heterozygous F_1 individuals had parents of distinct types. These are the grandparents of the final back cross generation, and may be designated P_1 . It is simplest to consider the situation in which such grand parental forms are homozygous. In the coupling phase, they would be AB/AB and ab/ab respectively. In repulsion they would be Ab/Ab and aB/aB . That is to say they are visibly distinct and, since we assume dominance, they are respectively of the same two classes as arise among their grandchildren.

It is clear therefore, that in order to study linkage fully it is necessary to possess information on three generations. For the parents of a back-cross segregating for coupling or for repulsion between a given pair of allelomorphs will appear the same. It is only when we examine their grandparents (P_1) in the double heterozygous line that we again find a distinction between them. Linkage therefore involves no association between particular genes as such, there is no tendency for example, for dominants or recessives to segregate with one another. Those genes which go into a cross together tend to come out of it together if they are carried in the same pair of chromosomes.

The theoretical examples of linkage so far considered are somewhat idealized, since they are instances of total linkage which, though known (in the male of the fruit fly *Drosophila*, for instance), is very uncommon. They do, however illustrate in a particularly simple way the manner in which the

chromosome mechanism can limit the operation of Mendel's second law. Yet the facts of cytology will suggest that linkage can rarely be complete. The interchange of sections of material between chromatids derived from homologous chromosomes, during the prophase of the first meiosis, must carry blocks of genes with them. Such a transference, being an interchange of material without an interchange of partners, is demonstrated cytologically by a chiasma. Genetically it produces crossing-over in which genes are transferred from one homologous chromosome to the other for the prophase chromatids (p. 149) become the daughter chromosomes of the second meiotic telophase. Consequently linked genes are not irrevocably associated together but can be combined in fresh ways, as can those carried in different chromosome-pairs.

Crossing-over may be defined as an interchange of linked genes consequent upon a reciprocal transference of blocks of material between chromatids derived from homologous chromosomes.

It will be well first to study crossing-over with the help of an example, and then to consider the general principles which it involves. Unfortunately very little is yet known of this important phenomenon in man, except in relation to the sex-determination mechanism (to be explained in Chapter II). Therefore it will be convenient first to examine its operation in another animal, and then briefly to discuss a human instance of crossing-over.

In rabbits a gene *Y* produces an enzyme which enables the animal to oxidize any xanthophyll which it eats. The recessive condition *yy* prevents the formation of this enzyme, so that the fat becomes yellow in animals supplied with green food. If this is not provided in the diet, the two conditions cannot be distinguished. Furthermore, albinism is recessive to normal coloration, and is due to the operation of a pair of genes *cc*. These are carried in the same pair of chromosomes as those determining yellow fat.

The character can easily be detected in living animals by scraping off little skin between the shoulder-blades, so as to expose the subcutaneous fat.

A homozygous normal rabbit (CY/CY) will produce gametes carrying $CY/$ while an albino with yellow fat (cy/cy) will produce gametes carrying $cy/$. If these animals, which constitute the P_1 generation, be mated, all the F_1 offspring will be normal in type but double heterozygotes of the constitution CY/cy . They will form gametes in which the two linked genes generally remain together giving the types $CY/$ and $cy/$ in equality. However crossing-over occurs between them approximately 14.4 times in 100 so that 7.2 per cent of the gametes become carriers of $Cy/$ while 7.2 per cent carry $cY/$. If such F_1 animals be mated with albinos with yellow fat, being the double recessive type cy/cy which produces $cy/$ gametes only a back-cross generation is obtained. This is composed of 42.8 per cent of normal offspring (CY/cy), and 42.8 per cent of albinos with yellow fat (cy/cy). Thus the two grandparental types have reappeared in equality. However 7.2 per cent of these back-cross animals are normally coloured, but with yellow fat (Cy/cy), and 7.2 per cent are albinos with white fat (cY/cy). These two groups, which represent a transference of the P_1 characters, are called the *recombination classes*. Together they measure the percentage-frequency of crossing-over. This is called the *cross-over value* (C.O.V.), and is obtained by adding together the two recombination classes and expressing them as a percentage of the total number of offspring. In this instance the C.O.V. = 14.4 per cent.

The example just described is one of Coupling. Repulsion could have been demonstrated by using homozygous fully coloured animals with yellow fat (Cy/Cy) and homozygous albinos with white fat (cY/cY) for the P_1 generation. An F_1 generation of normal, but double heterozygous, rabbits would have been formed as before. If this were mated to double recessives, albinos with yellow fat (cy/cy), a back cross would be produced. This would consist, once more, of the two grandparental types in equality each comprising approximately 42.8 per cent of the offspring (fully coloured animals with yellow fat (Cy/cy) and albinos with white fat, cY/cy), and the two recombination classes (normals, CY/cy ,

and albinos with yellow fat, cy/cy) also in equality comprising 7.2 per cent of the offspring each. This is repulsion, with a deficit of the double dominants and double recessives. The same groups appear as in the previous example, but their frequencies are reversed. However these remain approximately as they were in value, and the amount of crossing-over is still measured as 14.4 per cent by adding together the two recombination classes, though these are not the same as before. Once more we see that there is no association between the allelomorphs except that of their position on the chromosomes.

All the genes carried on a particular chromosome are of course linked with one another. It should therefore be possible to assign the linked genes of any organism to a series of groups. If the chromosome theory of heredity is valid, the number of such 'linkage groups' should equal the number of pairs of homologous chromosomes in the species. This proposition has been proved correct in all instances in which the genetics are sufficiently known to permit of testing it. Furthermore, when the pairs of homologous chromosomes differ from one another considerably in length, the size of the linkage groups varies roughly in proportion.

An important relationship exists between the cross-over values of three or more linked genes. If we consider three linked genes A, B, and C, the cross-over value between A and C equals either the sum of the cross-over values between AB and BC, or the difference between them. This condition can only be satisfied by a linear relationship, and it demonstrates that the genes are carried in a linear series along the chromosomes. Moreover it allows the correct order of the genes to be ascertained. Suppose the cross-over value between A and B is 4, and that between B and C is 1. Then the cross-over values between A and C will be either 5 or 3. If it be the sum (5), then the correct order of the genes is ABC; if the difference (3), the correct order is ACB.

The nearer together any two genes lie on a chromosome, the smaller is the chance that a break and interchange of material will occur between them. Therefore the cross-over

values provide a relative measure of distance. In our last instance, gene B lies four times as far from A as it does from C.

This last proposition will be strictly true for short distances only say under 8 per cent, for with a considerable length of chromosome the possibility of multiple crossing-over arises. When crossing-over occurs twice between two genes, the interchange produced by one is restored by the other. Thus the resulting double cross-over individuals are scored in the non-cross-over classes, so that the cross-over value is assessed too low but triple crossing-over raises it, and so on. However the effect of multiple crossing-over is not so considerable as might be anticipated, since the occurrence of one cross-over interferes with that of another in its neighbourhood: for crossing-over is determined in the chromosomes, and intertwining threads have a modal length of twist. Thus, for short distances, the cross-over value is not obscured by multiple crossing-over.

The tendency for one cross-over to prevent the occurrence of another in its neighbourhood is called *Interference*. It is measured by *Coincidence*. This is calculated as the actual amount of double crossing-over between any genes, divided by the amount expected. The expectation is the simple probability that two cross-overs should occur simultaneously. Thus, with a cross-over value of 20 per cent (obtained by adding together short lengths), the expectation, in the absence of interference, is that the apparent cross-over value should be about 16.8 per cent. Owing to interference it is found that the observed cross-over value falls short of 20 per cent, to a less extent than this.

It will now be evident that chromosome maps can be constructed from the data supplied by crossing-over. For the genes can be assigned to groups representing those situated on the same chromosome, while within these they can be placed in their correct order and at their relative distances apart. A map of part of a human chromosome obtained in this way is given on p. 51.

Apart from those linked genes associated with sex, to be

attention briefly to their chief characteristics, and for that purpose animal material will be more convenient than human at this stage.

Multiple allelomorphs usually control a given set of characters quantitatively so that they can be arranged in a series representing the degree to which their effects depart from the normal. In such a series, the normal condition is usually dominant to the others, but when two of the mutant genes are brought together they produce an intermediate result (pp. 84-5). It will be recalled that genes at the same locus are represented by the same letter using the capital for that giving rise to the dominant characters. The fact that a series of genes occurs at the same locus is indicated by giving the same letter to all of them and distinguishing the members by a suffix. The normal allelomorph is represented by the capital without a suffix. The mutant allelomorphs have small letters, the end term represented without a suffix. Should the normal be included, they are indicated by a suffix. Thus the amount of black in the house mouse is controlled by multiple allelomorphs: A^y (yellow belly), A (the normal uniform grey), a (black). Here the effect of the A^y is dominant to that of the normal (A), and A is dominant to it.

When animals possessing two different alleles are crossed, the offspring are of the type of the dominant allele. If the genes are not at the same locus, the dominant allelomorph of the other gene will be dominant even if the effects of the genes are different. For example, the recessive pink-eyed pig produces, in addition to the reduction in all the pigments of the body, a reduction in the skin. This is due to a pair of genes pp . If crossed with a similar effect except that the reduction is in the hair more particularly a reduction in the hair color, crossing these two types ($ppCC$) or

have the constitution $PpCc$. These are ordinary brown dark-eyed guinea pigs. On the other hand, the recessive white guinea pig with red eyes (strictly called the Himalayan type) is due to the operation of the genes $c^h c^h$ which are multiple allelomorphs of C c and of two others. Consequently on mating a red-eyed dilute animal ($c^d c^d$) and a Himalayan ($c^h c^h$), the normal condition is not restored among the offspring since, being allelomorphs, one gene does not bring in the dominant allelomorph of the other. The F_1 constitution is $c^d c^h$ and such individuals are intermediate between the two parental types. This result is diagnostic of the behaviour of multiple allelomorphs. It will further be evident that all the members of such a series have the same cross-over value with the other genes in their chromosomes.

We have now surveyed some of the essentials of Mendelian inheritance sufficiently for the purpose of this book. The fundamental distinctions between this and all other types of heredity which have been postulated from time to time will be considered in Chapter III.

CHAPTER II

THE GENETICS OF SEX

I. SEX DETERMINATION

SEX IS A quality which is inherited, and in a simple way. For the two contrasted characters involved, maleness and femaleness, with all their attributes, segregate sharply from one another in proportions which, in the adult (pp 53-5) are nearly equal. How complete this segregation may be is a matter of some dispute (pp. 86-8), but individuals obviously intermediate in structure between the two sexes, though known, are of great rarity. The mechanism which operates this system must briefly be considered.

The genes controlling sex are carried in a special pair of chromosomes called sex-chromosomes. The remaining chromosomes, collectively known as autosomes are not directly concerned in actual sex-determination (pp 84-5). In women, the two sex-chromosomes are similar to one another and they do not differ considerably from the autosomes, except that they bear, among others, the genes determining sex. They are called 'X-chromosomes'. Men, on the other hand, possess an unlike pair of sex-chromosomes. One of these is an X-chromosome derived from the mother while the other received from the father is an atypical chromosome carrying few genes, and none of them controlling sex. This is the 'Y-chromosome'. Thus in the human species, with a total of 48 chromosomes (24 pairs), there are 46 autosomes (23 pairs) and one pair of sex-chromosomes, consisting of two X-chromosomes in women and one X and one Y-chromosome in men.

During meiosis, the chromosome number is halved in such a way that each gamete receives one member of every chromosome-pair. Consequently in addition to the complement of 23 autosomes, all the eggs receive a single X-chromosome, while half the sperms receive an X and half receive a Y-chromosome. Thus the chances should be equal that

any egg, necessarily carrying one X-chromosome, is fertilized by a Y bearing sperm, so producing a male (XY), or by an X-bearing sperm, producing a female (XX) (see Fig 5).

Studies on animals possessing abnormal chromosome numbers have demonstrated that the X-chromosomes are

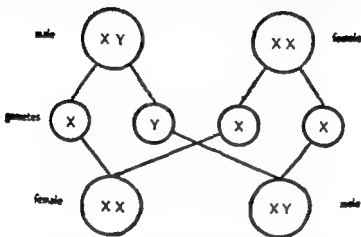


Fig. 5. The sex of an individual is determined by the number of X-chromosomes in its cells, one producing male and two producing a female. This should ensure the production of the two sexes in equality in the next generation. Note that the sex-control is quantitative, since the X-chromosomes are interchanged between the sexes at successive generations.

the actual agents deciding which sex shall develop. They have shown also that the Y-chromosome is generally without significance in sex-determination, save in certain groups: the Amphibia, for example. In some forms the Y-chromosome is absent, so that the chromosome number is odd in one sex and even in the other. But where, as is more usual, a Y-chromosome exists, its loss, owing to an abnormal cell-division, does not affect the development of the sex which should possess it.

It is worth while to reflect briefly upon these facts. We have seen that the control of sex depends upon the distribution of the X-chromosomes. Yet it will be observed that individual X-chromosomes are not restricted to any one sex. The single X-chromosome of a man, responsible for his sex, is derived from his mother where it was one of the agents concerned in making her a female; while a woman must necessarily possess two X-chromosomes, one of which she receives from her father in whom it had been male-determining (Fig 5). That is to say the X-chromosomes are constantly shuffled across from one sex to the other. Clearly they cannot be differentiated respectively as male- or female-producing structures. On the contrary their effect depends upon their number- the sex-determining mechanism is quantitative, not qualitative, in its action.

It is remarkable that the sex possessing the single X chromosome is not the same in all groups. For example, in mammals it is the male while in birds it is the female. Thus distinguishing names are necessary for the XY and XX types. The former is called the 'heterogametic sex' and the latter the 'homogametic sex'. In human (and probably in all mammalian) genetics 'heterogametic sex' and 'male' are equivalent terms, but this is not universally true in other animals. In man, therefore, it is the father not the mother, whose gametes determine the sex of his children.

Numerous genes are responsible for sex-determination in the Mammalia. Those carried in the X-chromosomes are female-determining, while others, in the autosomes, are male-determining. The dosage of the former is therefore variable (in one or two X-chromosomes), but that of the latter is fixed. The balance between these acts is so adjusted that the male-determinants, produced by the sex-genes in the autosomes, are in effective excess over the female-determining substances, produced by the sex-genes in one X-chromosome; but they are effectively deficient compared with double that quantity of the female-determining genes due to the presence of two X-chromosomes. It will be apparent, therefore, that though the sex genes carried in the

X-chromosomes act as the deciding elements in *sex-determination* (p. 33), others equally responsible for the *development of sex* are carried in the autosomes.

The embryological and physiological aspects of sex must now be related to the chromosome mechanism just described. The early embryo is capable of development either as a male or as a female, having a complete outfit of the rudiments required to build up one or the other type of sexual structure. An excess of male-determining genes, owing to the presence of but a single X-chromosome, causes the degeneration of the cortical, or ovarian, region of the gonad, and the development of its medullary or testicular element. The secretion of the male hormones from the interstitial cells of the testis ensures the growth of the male secondary sexual characters: vas deferens, penis, and associated glands. It also causes the retention of mesonephric material such as the epididymis, which is carried backwards with the descending testes. The same hormones bring about the degeneration of the Mullerian ducts and other pronephric structures. On the other hand, the excess of female-determining genes, due to the presence of two X-chromosomes, brings about the reverse set of changes owing to the formation of ovaries and the secretion of the female hormones from their interstitial cells. Thus the accessory sexual characters of both sexes are under hormonal control, being especially stimulated to develop at the time of puberty.

In Man, therefore, the chromosome outfit determines the type of gonad which shall develop, but only indirectly the secondary and accessory sexual characters through the intermediacy of the hormones from the testes or the ovaries. Yet this arrangement is by no means universal, for in many forms, the insects for example, all sexual characters are directly determined by the sex-genes. In such animals castration has no effect beyond sterilization, whereas the changes of puberty cannot take place in Man if castration has been performed early in life. Thus the voice of eunuchs remains high-pitched and infantile.

These facts have an important bearing upon the production

of hermaphrodites, a term which is commonly used to mean any mixture of the two sexes, of whatever kind. In the animals in which the gonads produce no hormones, and sex-characters are under the direct control of the genes, abnormal mitosis may greatly affect the sex of the individual. For this may lead to the loss of an X-chromosome in homogametic sex, or to the inclusion of two X-chromosomes in a cell of the heterogametic sex owing to the failure of daughter sex-chromosomes to separate at anaphase. If it takes place in an early cell-division, the products of abnormal cell may constitute up to one half of the body which is then of the opposite sex to that determined by fertilization. In this way male and female regions may develop side by side. Individuals in which this occurs are called gynandromorphs. They seem to be possible only with localized sex-control and cannot occur in Man, where the sex of the parts is not a function of the cells composing them but is under the central control of the gonad hormone.

In insects, furthermore, the action of the sex-genes may become quantitatively different in various geographical races. Within each race the necessary relationship is preserved that one or two X-chromosomes respectively carry an effective deficiency or excess of sex-genes. However, when races possessing different absolute values of the sex genes are crossed, the excess of the male or female sex-determinants may be insufficient, so producing another type of hermaphrodite called an 'intersex'. This is an individual which develops at first wholly as the sex appropriate to its sex-chromosome content, and subsequently switches over and develops wholly as the opposite sex. In male and female parts never form simultaneously: gynandromorphs and intersexes are sex intergrades in space and time, respectively (for a detailed account, see Goldschmidt 1933).

In intersexes of a slight degree, the characters of the inappropriate sex are those last to be developed, while early formed structures become progressively involved in the more extreme types. It is clear therefore that the ge-

control differentially not only the quantity but the rate of production of the sex-determining substances.

It is probable, but not certain, that this kind of intersexuality occurs in mammals. Races which have evolved independently may acquire different absolute values of their sex-genes. Crosses between them might therefore lead to an insufficient excess of one type over the other and, consequently to an incomplete suppression of the inappropriate portion of the originally ambivalent gonad. Subsequent hormone production might then be affected, so giving rise to sexual intermediates. But the human races do not appear to have differentiated sufficiently from one another before subsequent intercrossing to acquire such different absolute values of their sex-genes.

Another type of intersex is certainly known in some mammals. This is the freemartin of cattle: an individual of intermediate sex, which appears only as the twin of a normal male. In cattle twins, the embryonic membranes grow together and the blood-vessels anastomose, so allowing the blood and hormones from one embryo to circulate through the other. When the individuals are derived from separate eggs (dizygotic twins) they may be of different sexes. The testicular hormone, which is produced before the ovarian, then circulates through the female embryo, preventing the further development of the ovary and partially converting the secondary and accessory sexual characters to the male type. No such phenomenon is known in Man.

It is by no means clear to what the human physical aberrations of sex are due. Yet it is important to notice that though the sex-genes decide whether the gonads shall develop as testes or as ovaries, many other genes will determine the amount of hormone produced and its timing, as well as the response of the tissues to it. Such genes, as well as those directly concerned in sex-determination, can, of course, mutate to other allelomorphs, which will allow of segregation in the usual way. Some of the combinations so produced may cause a weak or abnormal response either to the male or to the female hormones, giving rise to instincts

inappropriate to the physical sex, perhaps combined with some slight tendency to approach the opposite sex in the proportions of the body or in the quality of the voice. So are some at least of the homosexuals: though the psychological attributes of that condition are very liable also to be environmentally produced, but doubtless more easily in some constitutions than in others. It is important also to notice that the development of the full sexual activities is reached gradually while genes exist which control the rate of processes in the body and the time of their onset (pp. 96-7); indeed the facts of inter-sexuality demonstrate that the action of the sex-genes is sometimes (and perhaps always) of this type. It is not surprising therefore to find that a phase of homosexual instinct is common in the adolescent even of sexually normal males and females. The length of time that such instincts persist varies, no doubt both genetically and environmentally. They may be prolonged into adult life, sometimes permanently but at others they are replaced ultimately by normal sexual reactions.

Gross abnormalities in the structure of the sexual organs, suggesting intermediacy are extremely rare in the human species, and they appear almost always to be in the direction of an apparent feminisation of males. But it should be noticed that the embryonic condition of the external genitalia is far more like that of the adult female than of the adult male. A mere retardation in male development may therefore give the impression of an approach towards the female type. Such an effect will usually be genetic, and the resulting abnormality is embryonic rather than hermaphrodite. It is probable, however, that true sexual intermediates are occasionally produced.

II. SEX LINKAGE

In the human species, the sex-chromosomes contain many more genes than those concerned with sex-determination. These affect the widest range of characters and bear no relation to sex, except that being carried in the same vehicle with the sex-genes they are distributed relative to them.

whereas sex is not related to the segregation of the ordinary autosomal genes which have been considered in the previous chapter. It has been explained (pp. 32-9) that genes carried in the same chromosomes are said to be linked because they assort together. Consequently those in the sex chromosomes are called 'sex-linked genes' and they give rise to sex-linked characters, owing to their association with sex.



Fig. 6. The human sex-chromosomes. The large X-chromosomes and the small Y-chromosomes each possess section (a-b) composed of homologous material. In addition there is a long section of the X-chromosome (b-c) which is not homologous with material in Y and short section of the Y-chromosome (b-d) which is not homologous with material in X.

The human X and Y-chromosomes are represented diagrammatically in Fig. 6. The greater part of the X-chromosome, from b to c in the figure, is not homologous with Y so that no crossing-over and consequent interchange of material, can occur in this region. However one short section of X is homologous with the greater part of the much smaller Y-chromosome (a to b in the figure), while a very short length of Y (from b to d) is not homologous with any material in X. Thus three types of sex-linkage occur in man, due to genes carried (1) in the non-homologous region of X (b to c), (2) in the homologous regions of X and Y (b to a), and (3) in the non-homologous region of Y (b to d). These must be considered in some detail.

(a) *Total Sex-linkage in the X-chromosome.* Genes carried in the section of the X-chromosome which is not homologous with Y are responsible for total sex-linkage in the X

chromosome. This is the most usual type and is the one always intended when sex-linkage is mentioned, except when stated to the contrary.

A notable example of such a sex linked character is provided by haemophilia. This is a disorder in which the blood fails to clot. The physiology of this condition is by no means clear. It may be due to a defect in the activation of prothrombin, but at any rate it does not appear to be associated with any structural abnormality in the capillaries (p. 43). The patients bleed profusely from cuts, though their 'bleeding time' is normal since the platelets are unaffected. Consequently even minor operations such as tooth extractions are associated with much danger. Slight blows may give rise to severe bruising and extensive haemorrhages under the skin. In addition, effusions of blood into the joints may gradually produce stiffness and constant pain, to deaden which haemophiliacs sometimes become drug-addicts. Such men usually die before the age of reproduction, but some may live to the age of twenty or twenty-five and produce children. The condition has attained considerable notoriety since it is rather widespread in the royal families of Europe.

Haemophilia is due to the operation of a recessive sex linked gene. A woman, heterozygous for it is therefore unaffected, since she carries the haemophilia gene (h) in one X-chromosome, and its normal allelomorph (H) in the other. Consequent upon meiosis, half the eggs which she produces will contain h , and half H only. She will usually marry a normal man, who has H in his only X-chromosome and produces in equal numbers X-bearing and Y-bearing sperms. From such a union four types of offspring will arise in equal numbers, though they appear only as three recognizably distinct classes, normal sons and haemophilic sons, and normal daughters. Of the latter one half are homozygotes, but the other half are heterozygotes who are carriers and can transmit the disease. That is to say normals and haemophiliacs appear in a 3:1 ratio, but this is not distributed at random relative to sex as have been the ratios considered in the previous chapters. On the contrary

half the sons but none of the daughters suffer from the abnormality (Fig. 7).

On the rare occasions when a haemophilic marries, his wife will usually be normal. All her eggs therefore carry H , while half her husband's sperm will contain a Y-chromosome and half an X necessarily carrying h . All the children

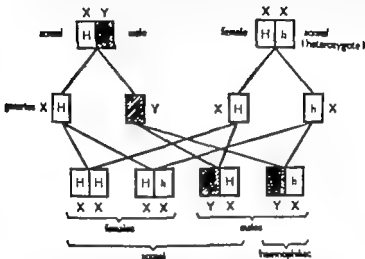


Fig. 7 Total sex linkage in the X-chromosomes marriage between man with dominant character and heterozygous woman. The gene producing haemophilia (A) is carried in the non-pairing region of the X-chromosome, and is recessive to the normal condition (H). The Y-chromosomes are shaded, the X-chromosomes are not.

will therefore be free from the disease, since the sons will inherit no X-chromosome from their father while every daughter receives H from her mother. However the daughters are all heterozygotes, capable of transmitting the disease in the manner already described. Here heterozygotes and homozygotes segregate in equal numbers but, once more, relative to sex, since the former type includes males, and the latter females, only.

A marriage between a haemophilic and a carrier should produce all four types of children in equal numbers: normal sons and haemophilic sons, normal (but heterozygous) daughters and haemophilic daughters. However no instance of a true female haemophilic has ever been recorded, though marriages of this kind are said to have taken place. As the character is recessive, two doses of the gene are necessary for its production in women, and it is possible that such individuals cannot survive until birth. The details of this form of segregation will be studied later (pp. 44-5) in relation to a condition in which all four types can actually be obtained.

It is highly important to notice that a normal woman can transmit haemophilia while a normal man cannot do so for he possesses only a single X-chromosome, carrying H . A man who is a member of a family in which haemophilia occurs may marry in confidence that his children will not inherit the disorder if he himself be healthy. In similar circumstances a woman can be given no such assurance. A normal woman who has a haemophilic brother should realize that the chances are equal that her children would completely escape the disease or that she would pass it on to half of them. Her affected daughters would be healthy though carriers, but her haemophilic sons would die at an early age. Further should a maternal uncle be a haemophilic, she may also be a carrier. Considering the female line only the chances that she is a heterozygote are evidently reduced by half for each generation since the most recent occurrence of the disorder: they are one in four if she has a haemophilic uncle, one in eight if she has a haemophilic great uncle. Yet the existence of normal brothers and uncles, in the female line, in generations subsequent to the last occurrence of the disorder may if sufficiently numerous, fairly dispose of the possibility that a woman is a carrier. It would not be unreasonable to consider her as free from the haemophilia gene if the number of such normal brothers and uncles amount in all to eight or more. Any woman who belongs to a family in which

haemophilia is known to have occurred should carefully consider these facts before she contemplates marriage.

The inheritance of haemophilia is illustrated by Queen Victoria and her family. She was herself normal but a carrier of haemophilia. Of her four sons, three were healthy and one (Prince Leopold) was a haemophilic who actually lived to contract a marriage and produce a daughter and a posthumous son. The occurrence of the disorder among her daughter's descendants has become a matter of history. It will be realized that the present English royal family is not subject to haemophilia since King Edward VII, being normal himself, could not transmit it.

A second and much rarer type of haemophilia also exists in which the symptoms are similar in kind, but milder. Affected individuals are not seriously inconvenienced by their disease and, though slight blows may result in considerable bruising, they are able to lead nearly normal lives. It is not unreasonable to anticipate the survival of female haemophiliacs of this kind, though the point does not seem to have been established. This mild haemophilia is inherited as a sex-linked recessive in the same way as the more frequent severe form. Moreover since the two types retain their characteristics in the different members of the families in which they occur, they cannot be attributed to an identical gene with variable effects (pp. 80-2). It is reasonable to conclude, therefore, that the mild form is due to another allelomorph at the haemophilia locus; if so, the haemophilia genes are members of a multiple allelomorph series. Precise evidence for this view is lacking, but its truth appears highly probable.

A purely analogous condition, called haemophilia-A, has also been reported (Levit and Malkova, 1930). It seems to be excessively rare, and differs from the true haemophilia both in its physiology and its genetics. In this disease the structure of the capillaries is defective. It is not an example of sex linkage, being autosomal and described as a dominant. But this latter statement is inaccurate (p. 17), since no homozygotes have been available for comparison, it is not

known if they would resemble the heterozygotes, or even if they can exist. Until further evidence is available, haemophilia A must be regarded as a heterozygous condition.

As already mentioned, certain aspects of sex-linkage cannot be studied on haemophilia, in which affected females are not known. They can, however be examined in a far milder and commoner affection, ordinary red-green colour blindness. In England this occurs in about 4 per cent of males and in about 0.4 per cent of females. It is inherited as a sex-linked recessive in the way just described (pp. 40-2) so that only those features not previously explained will now be considered.

If a colour blind man marries a woman heterozygous for colour blindness, normal and colour blind individuals will be distributed equally among both male and female offspring, the normal females being all heterozygotes (Fig 8). When colour-blind females marry normal males, all the sons naturally receive their only X-chromosome from their mother and thus carries the gene (*c*) for colour-blindness. The daughters obtain an X-chromosome from both parents, that from the father transmitting the normal allelomorph (*C*), dominant in effect. Thus all the sons are colour-blind like their mother and all the daughters are normal like their father (though they are heterozygotes): this is called 'criss-cross' inheritance. On the rare occasions when two colour-blind parents marry all their children must be colour-blind. There is some evidence that the gene for colour blindness is not fully recessive, so that sometimes the condition is at least partly expressed in the heterozygotes. Its frequency in women is therefore above expectation (pp. 121-3).

The genetics of colour blindness emphasize the important fact that there is no inherent barrier to the occurrence of a sex linked character in both sexes. This is in contrast with sex-controlled inheritance (p. 82), in which the characters concerned are limited to one sex for physiological reasons. However sex linked characters appear more frequently in one sex than the other: if recessive, they are commoner in the male; if dominant, in the female. The relative proportions

are discussed on pp. 121-3, but the mere fact is obvious. For a gene recessive in effect manifests itself whenever present in the male, but in the female it is dependent for expression upon the slender chance of distribution to the two X-chromosomes of the same individual. With dominant

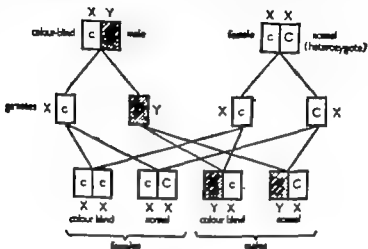


Fig. 8. Total sex-linkage in the X-chromosome marriage between man with recessive character and heterozygous woman. The gene producing colour blindness (c) is carried in the non-pairing region of the X-chromosome, and is recessive to the normal condition (C). The Y-chromosomes are shaded, the X-chromosomes are not.

sex-linkage, on the other hand, the presence of the two X chromosomes in the female allows a greater opportunity for the occurrence of the gene. Inheritance of this type is very exceptional, but a congenital absence of the incisors provides an example of it in which, however the heterozygous expression is variable. Its behaviour can readily be worked out from the information already provided in this section, remembering that the heterozygotes will be included in the classes manifesting the defect. However it is worth while to

known if they would resemble the heterozygotes, or even they can exist. Until further evidence is available, haemophilia A must be regarded as a heterozygous condition.

As already mentioned, certain aspects of sex-linkage cannot be studied on haemophilia, in which affected females are not known. They can, however be examined in a far milder and commoner affection, ordinary red-green colour blindness. In England this occurs in about 4 per cent of males and in about 0.4 per cent of females. It is inherited as a sex-linked recessive in the way just described (pp. 40-3), so that only those features not previously explained will now be considered.

If a colour blind man marries a woman heterozygous for colour blindness, normal and colour-blind individuals will be distributed equally among both male and female offspring, the normal females being all heterozygotes (Fig 8). When colour-blind females marry normal males, all the sons naturally receive their only X-chromosome from their mother and thus carries the gene (*c*) for colour blindness. The daughters obtain an X-chromosome from both parents, that from the father transmitting the normal allelomorph (*C*), dominant in effect. Thus all the sons are colour blind like their mother and all the daughters are normal like their father (though they are heterozygotes); this is called *criss inheritance*. On the rare occasions when two colour blind parents marry all their children must be colour-blind. There is some evidence that the gene for colour-blindness is not fully recessive, so that sometimes the condition is at least partly expressed in the heterozygotes. Its frequency in women is therefore above expectation (pp. 121-3).

The genetics of colour blindness emphasize the important fact that there is no inherent barrier to the occurrence of a sex-linked character in both sexes. This is in contrast with sex-controlled inheritance (p. 82), in which the characters concerned are limited to one sex for physiological reasons. However sex-linked characters appear more frequently in one sex than the other: if recessive, they are commoner in the male; if dominant, in the female. The relative proportions

are discussed on pp. 131-3, but the mere fact is obvious. For a gene recessive in effect manifests itself whenever present in the male, but in the female it is dependent for expression upon the slender chance of distribution to the two X-chromosomes of the same individual. With dominant

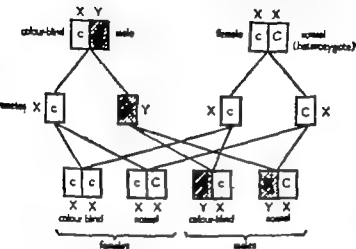


Fig. 2. Total sex-linkage in the X-chromosome: marriage between man with recessive character and heterozygous woman. The gene producing colour blindness (c) is carried in the non-pairing region of the X-chromosome, and is recessive to the normal condition (C). The Y-chromosomes are shaded, the X-chromosomes are not.

sex-linkage, on the other hand, the presence of the two X chromosomes in the female allows a greater opportunity for the occurrence of the gene. Inheritance of this type is very exceptional, but a congenital absence of the incisors provides an example of it in which, however the heterozygous expression is variable. Its behaviour can readily be worked out from the information already provided in this section, remembering that the heterozygotes will be included in the classes manifesting the defect. However it is worth while to

draw special attention to two of the situations to be revealed when this analysis is undertaken. First, if an affected man marries a normal woman, criss-cross inheritance in the opposite direction to that described on p. 44 occurs: all the daughters inherit the defect while all the sons are normal. Secondly when an affected (heterozygous) woman marries a normal man, normal and abnormal sons, normal and abnormal daughters, will be produced in equal numbers; for all the children receive one or other of the maternal X-chromosomes. Now it is important to notice that this particular result is not distinguishable from dominant autosomal inheritance, though the transmission of the gene in other circumstances will clearly indicate its sex linked nature.

It will be realized that all the normally sex linked genes, being those situated in the region of X not homologous with material in Y (Fig 6, b-c), are linked with one another. Crossing-over between them is of course possible in the female, in which this section appears twice, but not in the male, in which it occurs once only. A common affection such as colour blindness can be used in such linkage studies with the rarer sex-linked characters, and the linkage relations between it and haemophilia have actually been estimated (Bell and Haldane, 1937). The cross-over value proved to be about 5 per cent, so that the two genes are situated close to one another.

(b). *Partial Sex-linkage.* Genes situated in the homologous regions of the X and Y-chromosomes (Fig 6, a-b) differ genetically from the ordinary sex-linked type, discussed in the last section, in two respects. First, they can be transferred between these two chromosomes and, secondly they possess allelomorphs in both sexes, instead of in the female only. These are of course equal consequences of the existence of homologous material at identical loci in both types of sex-chromosome, but they have somewhat different genetic effects. Were their crossing-over entirely unimpeded, so as to give a C.O.V. of 50 such genes could not directly be distinguished from those carried autosomally. If on the contrary crossing-over between X and Y were very rare, so

as to escape observation in ordinary investigations, a dominant partially sex linked gene situated in X could not be distinguished from a dominant showing total sex linkage.¹ In similar circumstances, a recessive could not be confused in this way (see p. 48) owing to the second of the two propositions just stated, that it will possess an allelomorph in Y as well as in X. Partial sex linkage can now be illustrated by examples.

Retinitis pigmentosa may be produced by the action of any one of at least five genes (p. 75). Two of these are partially sex linked, one being dominant and the other recessive in effect. They all give rise to a somewhat variable group of symptoms. These include night blindness and a gradual contraction of the visual field, often leading to total loss of sight. They are associated with an attenuation of the retinal blood-vessels and a deposition in the retina of pigment which has migrated from the tapetum. This is visible with the ophthalmoscope.

If dominant retinitis pigmentosa were totally sex linked, men who suffer from the disease would transmit it to all their daughters and none of their sons. Actually however, they may carry the gene responsible for it either in their X or their Y-chromosome. If the former sex-linkage of the normal type will ensue, except that occasional affected sons will appear owing to crossing-over between X and Y. In the latter situation, with the gene already in Y the sons will chiefly be affected and the daughters free from the disease. But exceptions will also arise, leading to the production of a few normal sons and affected daughters, owing to an interchange of the gene in Y with its normal allelomorph in X.

When a woman suffers from retinitis pigmentosa if the kind now under discussion, she will almost always be heterozygous for the gene producing it. Her children will include both normal and affected sons and daughters: the four types appearing in equal numbers, whether crossing-over occurs or not. For that process merely transfers the gene from one

When situated in Y it might be confused with total sex-linkage in that chromosome, see pp. 51-2.

to the other of the maternal X-chromosomes. Consequently the autosomal, the partially sex linked, and the totally sex linked conditions are not distinguishable when a gene dominant in effect is transmitted by a woman.

The analysis of a recessive partially sex-linked condition is a little less simple. Affected individuals must receive the gene responsible for it from both parents. In the mother it must be carried in an X-chromosome, in the father it may be carried either in X or in Y. Consider these two alternatives. If no crossing-over occurred, half the daughters but none of the sons would be of the recessive type if the gene is carried in the paternal X-chromosome; but if in the paternal Y the reverse would be true. But crossing-over may transfer the gene from one paternal sex-chromosome to the other leading to exceptions: that is, to the appearance of the recessive character in occasional sons on the one hand or in occasional daughters on the other.

Thus recessive partial sex linkage will superficially resemble the autosomal system. From this it can be distinguished by an association with sex *within given families*. In some of these, affected males will be rare, and in others affected females. Thus it is only by the analysis of individual family records that such inheritance can be separated from the autosomal form. Were the cases in the population as a whole to be pooled for study the excess of males and of females would balance each other so that no indication of sex-linkage could be obtained.

Seven recessive pathological defects are now known, or on good evidence presumed, to be partially sex linked. These must briefly be described. They were all originally regarded as autosomal recessives, but it is now clear that the first five are associated with sex, though this is rather less certain for the last two of those to be listed.

(1) Recessive retinitis pigmentosa presents the same features as the dominant type already described. There exists also another recessive, but autosomal form, which is clinically distinct from all others since, in addition, it produces deafness.

(2) Xeroderma pigmentosum is a condition in which the skin is exceptionally sensitive to light, owing probably to some metabolic disturbance. It is usually recognizable a few weeks or months after birth. Exposure to sunlight causes reddening of the face and hands. This is followed by the development of severe freckles which do not disappear even when the skin is shielded from the light for long periods. These freckles become larger more numerous, and more deeply pigmented. Later warts arise and patches of skin become atrophic; while corneal ulcers make their appearance, to be followed by opacities. The patients shun strong light, and though the skin may be unhealthy over most of the body it becomes grossly abnormal only in the exposed areas. All attempts to ward off the ultimate consequences of this disease are unavailing: sooner or later multiple malignant changes take place in the skin, the conjunctive, or the cornea. These usually give rise to basal-celled carcinomas with only a very small tendency to metastasize. They can be kept in check for a time by repeated operations and radium treatment, but eventually they become uncontrollable and the patient dies of cancer of the face.

It appears that xeroderma pigmentosum is not quite recessive, for there is evidence that the heterozygotes may develop exceptional freckling. It is doubtful if a very heavily freckled individual should have children if a member of a family in which xeroderma pigmentosum has occurred; unquestionably such a person should not marry a relative (pp. 134-5).

(3) Congenital total colour blindness is an exceedingly rare state usually associated with various minor ocular defects. It is a much more extreme condition than ordinary red-green colour blindness, and the general colour perception is at least grossly impaired.

(4) It has been shown by Mather and Philip (1940) that hare-lip and cleft palate is a recessive condition which can be produced by either of two genes having apparently similar effects. One of these is autosomal, the other is partially sex-linked.

to the other of the maternal X-chromosomes. Consequently the autosomal, the partially sex linked, and the totally sex linked conditions are not distinguishable when a gene dominant in effect is transmitted by a woman.

The analysis of a recessive partially sex linked condition is a little less simple. Affected individuals must receive the gene responsible for it from both parents. In the mother it must be carried in an X-chromosome, in the father it may be carried either in X or in Y. Consider these two alternatives. If no crossing-over occurred, half the daughters but none of the sons would be of the recessive type if the gene is carried in the paternal X-chromosome; but if in the paternal Y the reverse would be true. But crossing-over may transfer the gene from one paternal sex-chromosome to the other leading to exceptions: that is, to the appearance of the recessive character in occasional sons on the one hand or in occasional daughters on the other.

Thus recessive partial sex linkage will superficially resemble the autosomal system. From this it can be distinguished by an association with sex *within given families*. In some of these, affected males will be rare, and in others affected females. Thus it is only by the analysis of individual family records that such inheritance can be separated from the autosomal form. Were the cases in the population as a whole to be pooled for study the excess of males and of females would balance each other so that no indication of sex linkage could be obtained.

Seven recessive pathological defects are now known, or on good evidence presumed, to be partially sex-linked. These must briefly be described. They were all originally regarded as autosomal recessives, but it is now clear that the first five are associated with sex, though this is rather less certain for the last two of those to be listed.

(1) Recessive retinitis pigmentosa presents the same features as the dominant type already described. There exists also another recessive, but autosomal form, which is clinically distinct from all others since, in addition, it produces deafness.

As explained in Chapter I, the cross-over value provides an estimate of distance, so that it is possible to construct a map of the pairing portion of the sex-chromosomes. This has been done by Haldane (1936) see Fig 9- it is the only human chromosome map so far available. Though somewhat tentative, it indicates the actual order of five of the known genes upon the chromosome and provides an estimate of their relative distances apart.

(e). *Total Sex-linkage in the Y-chromosome.* The non-homologous region of the human Y-chromosome is very

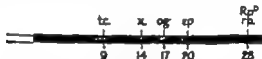


Fig. 9. Map of the pairing portion of the human sex-chromosomes, showing the position of five of the known genes carried on it. The beginning of the non-homologous region is represented unshaded. This may be either part of the long non-pairing section of X or the short non-pairing section of Y. The cross-over values are calculated from the point where the non-pairing and the pairing regions meet (x = total colour-blindness; x = xeroderma pigmentosum; og = Oguchi's disease; ep = recessive epidermolysis bullosa; Rpd and rp = dominant and recessive retinitis pigmentosa). After Haldane.

short, so that it must carry relatively extremely few genes. Such have been detected in two or three instances. One of them is responsible for the production of webbed toes, but it is known that several other genes, carried elsewhere on the chromosomes, may also give rise to this condition. An additional instance is provided by an extraordinary disease (ichthyosis hystrix gravior) in which the skin becomes thick, rugged, even bristly and blackened. It forms a tough cuticle which is shed at intervals, exposing skin which is at first normal but soon becomes thickened again. The affection has been encountered only in a single family.

Genes carried in the non-pairing region of the Y-chromosome are passed directly from father to son and, of course,

can only affect males. This is the sole instance of inheritance restricted to one sex; nothing comparable with it has been found, nor is to be expected, in women. Characters which are expressed in males, or females, alone may be instances of sex-controlled inheritance, dependent upon genes carried anywhere on the chromosomes (p. 82). However those which are also transmitted only by males must be due to genes carried in the non pairing section of the Y-chromosome. Thus a few characters must exist which are passed only down the male line, but female inheritance of this kind is not known.

III. THE SEX RATIO

The simple distribution of the X and Y-chromosomes would seem to ensure equality in the number of male and female conceptions. This expectation is not fulfilled and, indeed, the relative proportions of the two sexes vary at different times of life and in different circumstances. These facts, when analysed, throw light upon several social and medical problems. In preparing the following survey of them I have drawn largely upon the excellent account of Crew (1937), to which reference should be made for more detailed information.

The sex ratio is usually expressed either as the number of males to one hundred females, or as the percentage of males in the population concerned. Thus a sex ratio of 100, or of 50 per cent, indicates numerical equality. Consequently males are in excess when the sex ratio is high (over 100, or above 50 per cent), and females are in excess when it is 'low' (under 100 or below 50 per cent). The sex ratio at conception and at birth is called the primary and the secondary sex-ratio respectively. That at sexual maturity is often called the tertiary sex ratio in other animals, but in man the expression is too inexact to be useful.

The Report of the Registrar-General for 1935 shows that in England and Wales there is a slight excess of male births, the secondary sex ratio being 103/100 (51.2 per cent). This is progressively reduced, so that numerical equality

is reached in those aged from fifteen to nineteen years. In the next five-yearly age-group, of twenty to twenty four years, females predominate for the first time, and they become proportionately commoner in the population until there are actually twice as many women as men among those aged eighty five and over.

The differential elimination of males indicated by these data is apparent also in pre natal life, for the sex ratio of foetuses dying during the seventh to ninth months of intra uterine life is higher than at birth, being 110 (or 53.8 per cent). Indeed there is evidence that this is not only maintained but intensified in passing backwards towards conception. Thus the sex-ratio of infants dying during the first year after birth is highest for the very young while, according to Crew (1937) it is higher also among early than among late abortions. We may fairly conclude, therefore, that the primary sex-ratio departs widely from equality in the direction of an excess of males.

It will now be convenient to study somewhat further the results of this trend, then to seek an explanation for it, and finally to consider the problem presented by the high primary sex ratio.

The lower viability of males than of females is responsible for the way in which the sex ratio differs in varying circumstances since, within certain limits, unfavourable conditions tend to accentuate and favourable ones to mask it. There is ample opportunity for the secondary sex ratio to be affected in this way since, on the average, only 76 per cent of conceptions yield living offspring.

The secondary sex-ratio is highest among first born children, since abortion and miscarriage are relatively more frequent in large than in small families. It is lower among the children of old than of young mothers, for with advancing age the internal environment becomes less favourable for the foetus. As abortion is more frequent in urban than in rural communities, the secondary sex ratio is lower in towns than in the country. For obvious reasons also, abortions and

still births are particularly common in respect of illegitimate children, whose secondary sex ratio is consequently low. It is often stated that a relative increase in male births takes place in time of war. If this be a fact, and the evidence for it does not appear to be conclusive, it is possibly due to the wider spacing of births owing to absentee husbands. For repeated conceptions, following too rapidly upon one another create an unfavourable environment for the developing foetus. However any detectable effect of this kind appears rather to follow the conclusion of hostilities. Thus it may well result from the fact that there is an excess of first born children at this time (who, as already mentioned, have high sex ratio), owing to the frequent postponement of marriage during war. All factors which tend to reduce the standard of living tend also to lower the secondary sex ratio, which is higher in the upper and middle classes than among unskilled labourers. Consequently as stressed by Crew changes in the secondary sex ratio can be used as an index of the effectiveness of social services, such as slum clearance and attempts to improve the general health of the community.

All these facts are dependent upon the higher death-rate of males than of females, the basis of which merits inquiry. Clearly the more exposed and dangerous lives led by men than by women must contribute to the excess of the latter in the higher age-groups, though it must be remembered that deaths at childbirth tend heavily in the opposite direction. But such considerations are inapplicable to infancy and to pre-natal existence, so that other and more fundamental causes must be sought for the phenomenon.

The XX, XY chromosome mechanism itself constitutes a system which acts unfavourably upon the heterogametic sex. As will be explained in Chapter IV disadvantageous genes tend to become recessive in effect. Now if we exclude the small section of X homologous with Y it can be said that recessive sex-linked characters are always expressed in men but very rarely in women. The reason for this is obvious. The recessive sex-linked genes in a single X-chromosome

cannot be opposed by a dominant partner as they will usually be when two X-chromosomes are present (see pp. 40-1). The region of X which is not homologous with Y must contain many hundreds of genes, a few of which will almost certainly be in the recessive state in any individual and capable of lowering his resistance to disease or reducing his efficiency in other ways.

It will be noticed, however that these considerations apply not to the male as such but to the heterogametic sex. Yet it is found that the male is still the more heavily eliminated in those forms (e.g. birds and Lepidoptera) in which the female is the XY type, but to a less extent than in the reverse condition (Crew 1937). This suggests that while sex-linkage is a cause of the lower viability of the male in man, it is probably not the only one. Some additional agency a function of sex itself, must also contribute to it, and very possibly this is to be found in the higher basal metabolism of men than of women, which affects both the young (Benedict and Talbot, 1921) and the adult (Benedict and Kemmer, 1915). It is probable that the greater expenditure of energy by the male makes him less resistant and more liable to death than the female, a view which is supported by various experiments on lower forms (see Crew 1937).

There remains the extraordinary excess of males at conception, despite the operation of a mechanism which appears so certainly to ensure the numerical equality of the sexes at that time. This anomaly has satisfactorily been explained by R. A. Fisher (1930a, pp. 141-3) during the course of his valuable analysis of the effect of natural selection upon the sex ratio. Before reviewing this, it is necessary to point out that in lower forms genes are quite well known which act differentially upon the X and Y bearing gametes produced by the heterogametic sex. That studied by Gerabson (1928) in the fly *Drosophila pseudo-obscura* may especially be mentioned. This eliminates nearly all Y-bearing sperms, and is quite common in nature. It is highly probable that such genes are of almost universal occurrence, so that even the primary sex-ratio is susceptible to selection.

Bearing this fact in mind, the course of Fisher's argument is clear. He points out that the parents of almost all animals expend nutriment, as well as time or activity upon their young before these become independent. Natural selection will act on the parents to make this expenditure as efficient as possible. Now the reproductive value of an entire generation of offspring at the time when parental liability ceases is the same for the two sexes whatever their proportions may be, since each sex supplies half to the ancestry of future generations. Thus natural selection will so adjust the sex ratio that the total expenditure incurred on behalf of the two sexes shall be equal. But such expenditure must include not only the parental output upon those individuals successfully reared but also that lavished, and wasted, upon those dying before it ceases; so that in man, where more sons are eliminated than daughters, males are more expensive to produce than females. The average expenditure is therefore less for each boy born, and greater for each boy reared, than for girls at corresponding stages. Consequently in view of the equality of total expenditure, natural selection must lead to a condition in which boys are the more numerous at conception to a sufficient extent to make them more numerous at birth but less numerous before the end of parental care. The sex-ratio at the time when this ceases will not be affected by subsequent differential elimination, but such elimination will have modified the sex ratio when actual maturity is later reached. However as the total reproductive contribution of the two sexes is then still equal, the rarer sex will be the more valuable, so that more intense selection will be exerted towards its preservation. Thus it appears that marked inequality of the sex ratio at maturity will only arise if this condition is of decided adaptive significance. The system here outlined is of the widest application, and it will be observed that the human situation falls rather accurately within the limits which it imposes.

CHAPTER III

MUTATION AND THE NATURE OF HEREDITY

I. MUTATION

MUTATION MAY BE defined as the inception of a heritable variation. Changes in the genes themselves, or in the chromosomes which carry them, may be reflected in the characters of an organism, causing it to differ from the normal form. Since such changes affect the hereditary material they can be transmitted to subsequent generations, so that the characters which they produce are inherited. It will be evident that mutations may not have an immediate influence, as when one member of a homologous pair of allelomorphs mutates to produce a gene recessive in effect. Many generations may then elapse before a homozygous recessive arises, so that the appearance of an individual possessing a novel recessive character may indicate only the occurrence of a mutation in the distant past. On the other hand, an individual possessing a dominant character new to the stock which is being investigated usually demonstrates that a mutation has taken place in the germ-cells of one of its parents.

It is desirable to adhere strictly to the definition of mutation adopted here. Mutations are sometimes defined as changes in the genes; yet this is far too restricted, for chromosomal modifications lead also to inherited variations. Furthermore, the concept that some diversity exists in the germinal material is implied in all theories of inheritance, and so must be the inception of such diversity. It should therefore be possible to discuss the part assignable to mutation in the various hereditary systems postulated at one time or another and to compare it with that which it is now actually known to play.

It is unfortunate that the term mutation is often used in two senses: first, for the actual change in the hereditary material; secondly and quite incorrectly for the result of

that change. For instance, the less precise writers on genetics quite commonly refer to a gene which has arisen during the course of experimental work as a mutation. For this, the expression 'mutant gene' which may be said to give rise to mutant characters may be employed, and is unexceptionable. Further the word mutation is one which long antedates the development of modern genetics and, like many others now accurately standardised, has carried with it a tradition of inexact usage. Thus a novel character was originally described as a mutation though it might in reality be due to recombination or even to environmental variation. However when a term has acquired a definite technical meaning the fact that it was once employed less strictly is not an excuse for using it loosely to-day. Were this so, current nomenclature both in biology and in medicine would have to undergo a far reaching and wholly unnecessary revision. It should now be clearly appreciated that neither a gene nor a character can be called a mutation, only the act of change in a hereditary unit can so be described.

It has already been indicated that mutations affecting the hereditary material as we know it can be sub-divided into changes in the genes and in the chromosomes. These two aspects of the process must briefly be considered.

Gene-mutations must be due to chemical changes occurring at particular loci. These may be of various kinds, leading to the production of a series of multiple allelomorphs. As far as is known, the mutations at a given locus are limited in type, for they produce alterations in the same set of characters, often of a quantitative nature. That is to say we do not find a gene controlling for example, eye-colour but not height mutating to a condition in which it controls height but not eye-colour. Thus the chemical substitutions which a gene can undergo appear to be restricted, and it is this fact which enables us to say that the allelomorphs determine contrasted characters.

Chromosome mutations can be grouped into two main classes: abnormalities in the distribution of whole chromosomes, and chromosome fragmentation. The first of these

can again be subdivided into *polyploidy* in which the whole set of chromosomes is multiplied, and *heteroploidy*, in which a chromosome may be added to or lost from a single chromosome-pair.

Polyploids arise from failures in cell-division during meiosis, leading to the formation of a gamete with the diploid (unreduced) chromosome number. This, on fusing with a normal haploid gamete, produces a 'triploid' zygote possessing three, instead of two, sets of chromosomes. Further irregularities, such as the fusion of two diploid gametes, may lead to the production of individuals with four chromosome sets (tetraploids) or even higher chromosome values. On the other hand, haploid individuals may sometimes arise possessing a single chromosome set only as in the gametes; but this occurs by a different means, through 'parthenogenesis'. A spermatozoon which fails to achieve fertilisation will occasionally stimulate an egg to develop, and the individual which it produces will possess a single maternal chromosome set only. Polyploids have not been encountered in Man and indeed they are always rare in animals, though they are important and widespread in plants.

Heteroploids can rarely establish themselves, for the addition or loss of a single chromosome has greater and more harmful effects than the addition or loss of a complete set. This is due to the lack of genetic balance which ensues from quantitative variations in part only of the hereditary material. Doubtless the condition is very rare in man. However it is obvious that the addition of a Y-chromosome will have far less effect than that of an autosome; for part of the Y-chromosome is inert, while such genes as it contains cannot be necessary for life since women are without them. There is indeed some evidence that the two human X chromosomes have occasionally become attached, so that both must pass into a single gamete. When this is fertilised by an X-bearing sperm the resulting zygote dies owing to the lack of genetic balance which ensues, but when fertilised by the Y-bearing type it is clear that heteroploids possessing three sex-chromosomes (two X and one Y) can arise, and

there is evidence that they have actually done so in man. This of course produces a reversal of sex linkage, since the daughters receive both X-chromosomes from their mother and the sons receive their only X-chromosome from their father. At least one pedigree of this kind has been reported (Haldane, 1932b) in which the normal association between ordinary recessive colour blindness and sex was reversed.

Chromosome fragmentation may lead to the loss of part of a chromosome (deletion), the portion which remains is that which contains the spindle attachment. However the broken fragment may re-attach itself, the wrong way round (inversion) or else to the homologous chromosome (duplication) or to a non homologous chromosome (translocation). Such phenomena do not seem to have been studied in man, but they must certainly occur and a watch should be kept for them. They would most easily be detected as translocations to or from a sex-chromosome. If a sex linked gene were observed to become fully autosomal in inheritance, or the reverse, strong presumptive evidence of such translocation would be obtained, provided that it were possible to distinguish the occurrence from partial sex-linkage.

It is important to notice that in other animals, and in plants, numerous combined cytological and genetic studies of chromosome mutations have been made. For instance, genes have occasionally been found associated with the wrong linkage-group. In these circumstances it has often been possible to see that one chromosome is too short and another correspondingly too long, owing to the translocation responsible for the observed genetic irregularity. Such observations provide a remarkably complete demonstration of the chromosome basis of heredity (see Sinnott and Dunn, 1939; Waddington, 1939).

Very short deletions may give much the effect of gene mutations, nor can they be detected cytologically. On general grounds it is not to be expected that the majority of genic changes are due to an actual loss of material, and there is evidence that this is not so.

It should be noticed that mutations, whether of the gene or the chromosomal type, are strictly localized phenomena. The occurrence of a mutation at one locus does not affect the allelomorph, nor does it tend to produce mutations in the genes on either side of it. This latter statement may possibly have to be qualified, since a modification in the effect produced by the genes near the locus of a mutation has been reported in a single organism (the fruit fly *Drosophila*). On the other hand, it does not yet appear to have been established that such genes have also mutated. The alterations in the characters which they produce may be due to an interaction between their effects and those of the new mutant gene (Chapter IV); indeed it seems likely that this is so.

There is evidence that mutations are slightly more frequent during cell-division than in the resting-stage, but they are not in fact restricted to any one period of cell activity. Nor are they confined to the germ tract, but can occur in the body-cells also (*somatic mutation*). This is more important in plants, where somatic tissue can give rise to germ-cells throughout life, than in animals; but it has been widely established in both kingdoms. In man, the process is of potential importance since it may possibly initiate a malignant change (pp. 93-4). An example of it is probably provided by heterochromia iridis.

Of great theoretical importance is the fact that *reversion* can occur from the mutant gene to the allelomorph from which it was derived, from the abnormal to the normal. It is clear therefore, that mutations are not essentially destructive changes, from more to less highly organized states, or downwards from compounds possessing high chemical energy. This fact assures us that mutations as we encounter them are of a type suitable to initiate the genetic diversity of living organisms.

Mutations are exceedingly rare phenomena. Yet they are recurrent, and take place with characteristic frequencies, being relatively commoner at some loci than at others. It is probably true to say that one mutation in a million individuals is an approximate average mutation-rate for a

given gene. A mutation-rate of 1 in 50,000 individuals is exceptionally high and rarely exceeded.

These values appear to be approximately similar throughout the widest range of organisms, both animals and plants, and for this there is good reason (pp. 72-3). We may be confident therefore that they apply also to man. It is, however, a somewhat remarkable fact that we actually possess direct evidence of the human mutation-rate in respect of a few genes. The lines upon which such information has been obtained must briefly be indicated.

The first estimate of mutation-rate in man was obtained by Haldane (1935) from a study of haemophilia. It has been pointed out that this is a recessive sex linked disease of so severe a nature that nearly all haemophiliacs die without producing offspring (pp. 40-3). Two thirds of the X chromosomes of the human race occur in women and one third in men. One third of the haemophilia genes in the population are, therefore, always exposed to selection, and are nearly always eliminated, while the remainder are not. Thus were they not supplied anew by mutation, the disease would rapidly die out, and at a calculable rate. The frequency of mutation necessary to maintain haemophilia in the population can therefore be found. Haldane was able to show that the proportion of haemophiliacs living in Greater London in 1935 must lie between 36 and 175 per million male births. We may be confident that this proportion is in equilibrium, a conclusion easily accepted if we consider with Haldane, the situation in former times were this not so. Suppose mutations were not making up for the known elimination of haemophiliacs, so that the haemophilia genes now existing were derived from haemophiliacs or heterozygotes in an earlier population. Thirty generations ago haemophilia would be 100 000 times commoner than it is to-day and the whole male population of England would be haemophiliacs at the time of the Norman Conquest. Haldane calculates that 1 mutation in 50 000 individuals is required to balance the elimination of the haemophilia gene, which therefore represents its mutation-rate.

The study of epiloia has provided material for an investigation of mutation at another locus (Gunther and Penrose, 1935). This disease is one in which mental deficiency is associated with adenoma sebaceum and other skin defects (pp. 79-80). It is inherited as an autosomal dominant, yet a number of cases are known to have had normal parents. It is highly unlikely that these represent failures in heterozygous manifestation, since the segregation is always very clearly marked. Such sporadic occurrences must, in fact, be mutations, and Gunther and Penrose find that they take place with a frequency which lies between 1 individual in 60 000 and 1 in 120,000 of the population.

It is most important to notice that such estimates of human gene-mutation do not represent an average but approach the upper limit of its frequency. For evidence along these lines could not be obtained for mutation-rates much lower than those actually observed. It is clear therefore, that mutation in man is of the same order of magnitude as that in other organisms (pp. 61-2). In those instances actually studied, the frequency is slightly higher than of the most mutable genes of *Drosophila* (the gene for white-eye, with a mutation rate of 1 in 80 000 individuals), but does not fall very materially beyond this. Nevertheless, some indication of the more normal mutation-rates in man can occasionally be obtained. The males affected by mild haemophilia, which is allelomorphic to the severe form (p. 43), are handicapped to a comparatively slight degree and often become parents, though they must contribute somewhat less to posterity than do healthy individuals. Thus the selection operating against this gene is far less severe than that against ordinary haemophilia, yet the mild type is much the rarer. Consequently mutation to this gene must be very much more uncommon than to the other haemophilia gene, and a frequency of one in a million individuals is probably an overestimate for it. The significance of mutation-rate will be more fully discussed in the second section of this chapter.

It is not known what agencies are normally responsible for mutation. Indeed environmental influences are rarely

able to affect the hereditary material, and only those of the most violent kind can do so. H. J. Muller was the first to show that mutations can be induced by X-rays. In favourable circumstances, the mutation rate can be increased about 150 times by this means. It is now established that all types of short wave radiation are capable of producing mutations: X-rays of different lengths, ultra violet light, the γ -rays of radio-active substances, free electrons (β -rays of radium), and neutrons. These agents are all equally effective so long as equivalent doses (judged by ionization rates) are employed. Special allowance must of course be made for those of low penetrating power particularly ultra violet light. All forms of mutation, both genic and chromosomal, can be induced by these means, but entirely at random. As with the spontaneous type, they do not cause allelomorphous genes, or those at neighbouring loci, to mutate. No one agent tends to produce a given class of mutations, or to induce them at one locus rather than another, nor can the results be controlled by varying the dosage or by any other known means. Many of the mutations which take place are the same as those which have appeared spontaneously. Others have not been observed except as the result of artificial induction, but it is highly improbable that these are, in reality novelties. As such treatment increases the frequency of mutations so greatly some will naturally be encountered which have not yet been detected in normal circumstances. Furthermore, reverse mutation can be induced by short-wave radiation.

It is found that the relation which exists between the amount of radiation and the rate of induced mutation is of the simplest kind, being one of direct proportion. A doubling of the dosage results in the production of twice as many mutations. It is therefore possible to determine the frequency of mutation produced by any given amount of short wave radiation. That occurring naturally proves to be far too small to account even for the minute frequency of spontaneous mutation. Some other agency must be responsible for most of this, but its nature is not certainly known.

However some genes are able to influence the general level of mutation in the organism. Presumably they place the hereditary material in a chemical environment which promotes instability. Thus the mutation-rate is in part genetically controlled and it is therefore susceptible of selection, a conclusion of great importance.

It has now been possible to induce mutation by means of short wave radiation in a great variety of organisms both plants and animals, including insects (*Drosophila*, *Habrobracon*, and others) and mammals (mice). They all respond in a similar way. It may be added that in lower forms a small increase in the mutation-rate has resulted from the application of heat; but this is not likely to be an effective agent in mammals and birds, which possess a constant temperature control. However we can be certain that X-rays and radium induce mutation in man, and the uniformity of the effects which these agents produce on the widest variety of organisms allows us to generalize with confidence on their influence on the human hereditary material.

Since the vast majority of all mutations must necessarily be harmful (Chapter IV), that influence, we can be certain, is bad. Satisfactory data do not yet appear to be available on the proportion of miscarriages, abortions, and still-births among the offsprings of radiologists. Despite the protection afforded by modern technique, it is hardly possible that these conditions are not in some slight excess when compared with the rest of the population. They would, of course, arise from the production of mutant genes dominant in effect. A very different situation is presented by the recessives resulting from radiation mutations, and this matter has recently been studied by Muller (1941). The appearance of the homozygous recessive type may be due either to the mutant gene meeting another like it, which had been induced independently or to the meeting of two genes descended from the same original mutant. Muller investigated all the aspects of these two possibilities, including the frequency of induced mutation, the survival value of abnormal types, and the degree of inbreeding in human populations. He reached

the conclusion that even in the most closely inbred groups of modern society a recessive gene originating from radiation technique would remain latent for 600 and probably for several thousand years. Some potential danger from the accumulation of such genes in the population none the less exists, but it cannot of course outweigh the diagnostic and therapeutic benefits of irradiation. Yet it is well to draw attention to a fallacy which frequently finds support when such a situation as this is exposed: that the accumulation of harmful recessives arising by mutation, due in this instance to radiation therapy can have a deleterious influence upon human evolution. Under Mendelian inheritance, evolution is not controlled by mutation.¹ The use of radiation to-day may increase the proportion of disadvantageous types segregating in the distant future. These will be subject to counter-selection as they appear but they cannot influence the course of evolution. However when we consider the possible consequences, both immediate and remote, of the fact that short wave radiation induces mutations, the importance of shielding the gonads during radiation intended for other parts needs no additional emphasis.

II THE NATURE OF HEREDITY

It is assumed throughout this book that human inheritance is of the Mendelian type, although many other theories of heredity have been advanced. Such an assumption affects profoundly the deductions to be drawn from observations on inherited conditions in man, and the influence of the environment upon him. Consequently it is essential to review quite briefly the main lines of evidence which can be adduced in favour of so far-reaching a conclusion and to consider rather more fully than was possible in Chapter I, in what essential respects the Mendelian system of heredity differs from all others. It is necessary therefore, to embark upon a short discussion which, though theoretical, is not unpractical. Indeed I do not see that any just comprehension of human genetics can be attained without it. In a

¹ See Fisher (1930a), also the second section of this chapter.

previous work I have examined the nature of heredity from an elementary point of view in rather more detail than can be done here (Ford, 1938). However those who require a full analysis of this subject should consult the writings of R. A. Fisher, especially his fundamental work, *The Genetical Theory of Natural Selection* (1930s).

All hereditary systems can be classified as belonging to a few basic types, a fact which greatly assists in their analysis. First, inheritance may be either unisexual or bisexual. It has been widely held in the past that one sex only contributes the whole, or else the greater part, of the hereditary material to its offspring. Indeed the laws of most civilized countries to-day are, incorrectly constructed on the assumption of unisexual and paternal heredity though the concept of purely maternal inheritance has been upheld from time to time. In so far as it is possible to study the problem critically by observation or direct experiment, no support for unisexual inheritance has been forthcoming; thus the data of genetics indicate that, in bisexually reproducing organisms, the two parents are equally responsible for the hereditary characters of their offspring. However many forms, man for instance, are unsuitable for experimental technique, while the hereditary control of the majority of characters is far too complex for strict analysis. It is fortunate, therefore, that there exists a method for assessing the hereditary contribution of the two parents in the widest sense, provided only that it is possible to detect any measurable variability in the character under consideration. I refer to the study of correlation between a group of children and their male and female parents respectively.

Consider any character outside the scope of experimental treatment; human height, for example. Now it is possible to calculate a *correlation coefficient* which expresses the degree to which the variability of two characters is associated.¹ Suppose we obtain the correlation coefficients between the height of a group of fathers and their sons and, secondly

¹For the appropriate method for doing so, and for calculating the error involved, see Fisher 1941.

that between the same group of sons and their mothers. These two correlation coefficients measure the tendency for height to be associated in parents and offspring. Now if the hereditary contribution of males and females is dissimilar the two correlation coefficients so obtained will differ significantly. That they never do so indicates that the father and mother are of equal importance in inheritance. In addition, it should be noticed that a comparison of correlation in relatives and unrelated persons provides a proof of heredity and a measure of its intensity in instances outside the scope of experimental verification.

It is evident that the hereditary material must be transmitted in the germ-cells. It may also be asked, is it restricted to the nucleus, or to the cytoplasm, or is it carried in both regions? The answer to this question has just been given. Males and females contribute exactly equal shares to the nucleoplasm of the next generation, but the amount of cytoplasm which they provide is vastly different. It is not at all uncommon for the female to supply to her children a million times as much cytoplasm as the male, or more. Even the small human egg carries immensely more cytoplasm than does the sperm. Were the cytoplasm to play any significant part in heredity the contribution of the two sexes could not possibly be equal, which it is proved to be. The nucleus, not the cytoplasm, is the actual agent in transmitting the genes, whether we can demonstrate the fact by experimental breeding and cytology or not.

We can therefore limit organic inheritance to those systems which are bisexual and nuclear. Having done so, two possible types remain. Some sort of units, controlling the characters of the organism, must be transmitted from parent to offspring if heredity has any physical basis at all. Further, since the characters are controlled equally by the two parents, they must be determined by the action of pairs of factors

An obvious exception has to be made in unisexually reproducing organisms (often a secondary condition) in which, however the genes are still carried in the nucleus. A few examples of cytoplasmic inheritance are also known, but these represent special instances only.

(allelomorphs) derived respectively from them. Now when such pairs are dissimilar (heterozygous), it can be supposed either that they contaminate one another when brought into the same cell (blending inheritance), or that they remain permanently distinct (particulate inheritance). Numerous theories essentially depending upon blending have been advanced, but particulate inheritance is the Mendelian type.

It must clearly be understood that blending in this sense refers to the genes, not to the characters which they produce. It is a commonplace to find that genetic factors controlling contrasting characters evoke an intermediate effect when brought together. The characters have then blended; that the genes controlling them have not done so is demonstrated by the fact that in succeeding generations the contrasted types 'crystallize' out of the hybrid mixture pure as they were before, consequent upon segregation. The genes have remained distinct, whatever their effects have done, and this is particulate inheritance.

So long as it is possible to produce F1 and F2 generations and compare them, it can be decided whether inheritance is of the Mendelian type. For blending leads to uniformity while the particulate mechanism maintains diversity owing to segregation. If, therefore, the F1 generation is more variable than the F2, the inheritance involved is blending; while if F2 is more variable than F1, it is particulate. We are thus able to decide whether inheritance is Mendelian in instances which are far too complex for factorial analysis. F2 generations, as such, cannot normally be studied in man, since they involve incest. But the essential feature of them, the mating of two heterozygotes, is constantly observed. Furthermore, the F2 generation is merely the extreme instance of the proposition that a marriage between relations tends to cause variability through the segregation of homozygotes. The well-known tendency of recessive characters to appear more frequently among the children of closely than of distantly related parents is an expression of the capacity of the particulate mechanism to promote diversity and provides evidence of its operation.

We may therefore accept the conclusion that organic inheritance in man and other organisms is of the Mendelian type. A number of important consequences flow from this fact, but a few of them only are relevant to the purpose of this book, and these can be touched upon but briefly. With a system of blending inheritance, leading to uniformity inherited variability would be rapidly reduced at every generation, actually it would be halved. In such a situation we are faced with two alternatives: either the amount of inherited variability must be minute, or else it must be maintained by a flow of mutations so considerable as to counterbalance the influence of blending. This is the position with which Darwin was confronted in his analysis of evolution based, as it was, upon the concept of blending inheritance. It led him to make a careful study of organisms in nature and under domestication from which he determined that they possess abundant variability. This, therefore, he conceived must be supplied by mutation ('new variation'); consequently he attributed great importance to all agents controlling that process, either its type or its frequency. Under a system of blending inheritance the induction of mutation must be a matter of overwhelming significance, and Darwin was perfectly correct in adopting that view but it was falsely founded. Organic inheritance is not of the type that he supposed, for it is particulate; the contrasted allelomorphs do not contaminate one another when brought together into the same cell, and their segregation is sufficient to ensure the preservation of ample variation. With particulate inheritance, mutation not only can be but must be (p. 78) hundreds of thousands of times less common than Darwin thought it was, and agents controlling mutation are hundreds of thousands of times less important than Darwin thought they were.

It is now possible to consider the bearing of these facts upon human affairs. Evidently we can no longer attach significance to those theories of human evolution which work by controlling mutation. Such is the Lamarckian, involving the inheritance of the effects of use and disuse,

subsequently extended to cover the inheritance of those characters which are newly acquired during the life of the organism. Medical men may well be asked if we have any ground for assuming that the effects of the environment are inherited. The nature of organic inheritance, limiting as it does so severely the part assignable to mutation, precludes such a view. It should further be noticed that the concept requires in addition a qualitative control of mutation of a very remarkable and improbable kind, such that the environment should so modify the hereditary material as to cause it, through all the complexity of development, to reproduce the same set of characters which the original environmental stimulus chanced to evoke in the parental body. No such tendency has been detected, while a mechanism is not known, and hardly can be conceived, capable of producing it.

It has frequently been urged that environmental effects may be inherited even though it has not been possible to demonstrate this experimentally since laboratory tests are of short duration; for it may be that a process of this kind is none the less of importance during the immensely longer periods of time occupied even by minor evolutionary changes. It has, on several occasions, been pointed out that such a conclusion is false (see Haldane, 1932a, pp 127-8). If environmentally induced mutations produce advantageous characters, or even if disadvantageous, they are of high frequency. It should be possible to detect them within the course of ordinary experiments. But if these are uncommon, it can be shown mathematically that the genes to which they give rise cannot spread through the population in the face of even a very mild degree of selection. The most that such slowly acting agencies could do would be the production of completely unimportant characters of nearly neutral survival values.

In spite of all that has been said, some caution is necessary in assessing what may appear to be the effects of environment upon heredity. An example, of the type frequently encountered in medical practice, will make this clear. It is of course obvious that the children of drunken parents are

more likely to become alcoholics than are those of the abstemious, owing to the influence of their home life. But are children especially prone to become drunkards if they belong to a family in which there is a history of alcoholism? Unfortunately we can be fairly certain that they are, even if removed at once to the environment of a new home. For the tendency to develop a craving for alcohol is certainly in part, hereditary. Of direct importance, however is the conclusion that it is irrelevant whether or not one of the parents had given way to such a tendency before the birth of the children.

This discussion on the nature of heredity can be concluded by returning to the problem from which in effect it started, that of mutation rate in man. It was pointed out that there are good grounds for supposing the average human mutation-rate to be approximately the same as in other animals and in plants, and that even at its highest it hardly exceeds that of the more mutable genes in the fruit fly *Drosophila* (pp. 62-8). This uniformity of the mutation-rate in organisms having greatly different lengths of life is a highly remarkable and significant fact. As already mentioned, mutation is not restricted to any one period in cell activity. Consequently it should be measured per unit of time; its frequency per generation should be irrelevant. Yet this perfectly logical expectation is not fulfilled. Haldane (1933) showed that if we take fourteen days and thirty years as reasonable average lengths of a generation in *Drosophila* and man respectively the upper level of human mutation of about 1 in 50,000 (for the haemophilia gene) when adjusted for time is equivalent to a mutation rate of 1 in 40 000 000 per *Drosophila* generation, a value so minute as to fall outside anything we know of mutation in that organism. Judged per generation, man has nearly the same mutation rate as *Drosophila*, judged per year *Drosophila* is immensely more mutable than is man.

We may well marvel at the astonishing relation between the mutation-rate and the generation, irrespective of its length, revealed by these facts, yet its explanation is not

difficult to find when we recall that all inheritance is Mendelian. The great value of this system, when compared with any blending mechanism, is the permanence of its hereditary units. This enables selection to favour even minute advantages and allows an organism to make use of genes which arose far apart in time or in space, so escaping the "swamping effect of intercrossing" which proved so great a stumbling-block to Darwin, on his assumption of blending (Fisher 1930a). But this crowning advantage of the particulate system is wholly discarded if mutation be common. The vital permanence of the genes is then lost, even though they do not contaminate each other. With Mendelian inheritance, mutation not only need not, but must not, be frequent. Selection must restrict the occurrence of mutation per generation sufficiently to ensure a high degree of permanence to the genes. Its average admissible limit will be a given frequency per generation, to ensure which the frequency per time between organisms having long and short life-cycles must be vastly different. Thus the human mutation-rate is in accord with the Mendelian, and with no other system of heredity: while its similarity per generation to that of other organisms demands the fundamental action of selection in a manner which must affect profoundly and in diverse ways, the analysis of human heredity

Y
17-1-34
393

CHAPTER IV

THE ACTION OF THE GENES

THE PREVIOUS CHAPTERS of this book have been restricted to a discussion of the behaviour of the genes, their segregation and mutation, and of the effects to which they give rise. For this purpose particular genes have been treated merely as the inherited basis of given characters. It is, however, important to bridge the gap between genes and characters, and to determine what type of effects the genes may have and the ways in which they produce them, to obtain, in fact, some information on the physiology of genetics. This we shall now attempt.

Physiological genetics is a subject which has made great advances during the last twenty years, but its data are derived almost exclusively from non-human forms: from other animals and from plants. Yet it is one of direct and practical importance in man, so that some endeavour must be made to indicate a few of its more important results. At first sight such a task appears very unpromising owing to the scarcity of suitable human examples, but it is facilitated by the very wide application of the principles of genetics. When we find that a particular phenomenon occurs in such diverse forms as rodents and insects, dicotyledonous and monocotyledonous plants, rather tenuous evidence for its existence in man may be the more readily accepted.

The poverty of the data bearing directly upon the physiology of human genetics is due to three causes. First, the small amount of attention which has so far been paid to the subject: a great deal more relevant information could be accumulated even in the present state of our knowledge. Secondly the fact that much of such data must be derived from experiment, and this is restricted to the most meagre limits in man. Thirdly since man belongs to the Mammalia, he is a member of a group protected against the effects of the

environment to an extraordinary degree. Compared with the majority of animals and plants, the possibility of examining the action of the genes in different conditions is in that class reduced to a minimum. We may therefore attempt to study the effects of the genes, and their interaction with the environment in the widest sense, having at the outset recognised the great handicaps necessarily imposed upon such an inquiry

1. THE EFFECTS OF THE GENES

Certain types of genetic effect may usefully be classified before attempting to consider the behaviour of the genes in varied environments. It will then be possible to give a brief account of the dominance phenomena, and of a few instances in which genetic action has been analyzed from the physiological point of view

Attention has already been directed to the fact that distinct genes may have nearly or completely identical effects. Thus *retinitis pigmentosa* (p. 47) may result from the operation of five, or more, different genes. Of these at least two are autosomal, one being dominant and the other recessive in expression, one is recessive and totally sex linked, while two, one dominant and one recessive, are partially sex linked and probably allelomorphs. Only the autosomal recessive is distinguishable in its effects since, unlike the others, it produces deafness in addition to the characteristic changes in the eye. A number of similar instances might be given, such as *keratosis follicularis* (Darier's Disease), which has been produced by a sex-linked gene, though the disorder is usually inherited as an autosomal dominant. However it appears unprofitable to reduplicate examples save in special circumstances. Distinct genes may also produce effects which are very similar in kind but different in degree, thus resembling the series of characters to which multiple allelomorphs give rise (p. 30). Attention has already been directed to the three forms of *epidermolysis bullosa* (Chapter II), which are characterized as mild, dystrophic, and severe dystrophic. Yet these are not the result of allelomorphs but are due to

three genes at least one of which is known to occupy a distinct locus. The first two are autosomal dominants, that producing the dystrophic form being rather irregular in expression, while the third, responsible for the severe dystrophic condition, is recessive and partially sex linked (p. 80).

The instances so far given of genes having similar effects relate to rare abnormalities, and I know of no occasions on which they have been brought together in the same individual. Were this to occur several distinct possibilities arise, but only two of them require consideration at this stage: that is to say the results might or might not be cumulative. Numerous instances are known in animals and plants in which characters due to the operation of genes have been combined, sometimes without increasing their effect. Thus the 'rex' rabbit is one in which the stiff guard-hairs are greatly reduced, producing a plush-like coat of commercial value. The character is recessive and it may be due to the action of any one of three genes, two being linked and one carried in a different chromosome. Their effect is the same whether one, two, or three of the homozygous recessives are present. I am not acquainted with any definite example of the same type in man, though doubtless such exist.

More often, genes producing similar characters are additive in their action. This is undoubtedly very frequent in man, particularly in respect of quantitative differences. An excellent example is provided by human height. It can be demonstrated by means of correlation (p. 67) that this is partly hereditary. But marriages between tall and short parents give rise to no clear-cut segregation, owing to the fact that height is controlled by many genes producing small cumulative effects. When a character determined in this way is studied in those animals or plants in which a large progeny can be reared, it is found that the majority of the offspring approximate to the average height while the more extreme forms become progressively rarer the proportions bearing a definite relation to one another such that the

whole group falls within a curve of normal distribution.¹ This applies not only to the F1 but also to the F2 generation, in which the curve remains 'unimodal' that is to say it gives no indication of segregation into different classes. Such a condition is known as continuous variation. It must not be supposed, however that the inheritance involved is non Mendelian. Indeed the analysis of heredity undertaken in the latter part of Chapter III can admit of no such view. That it is determined by the particulate mechanism is demonstrated by the fact that in these circumstances the F2 generation is more variable than the F1 (p. 69): the inheritance being 'multifactorial'.

It is plain that we have here the occurrence of gene interaction, in the sense that a number of genes, operating quantitatively are required to produce a given effect. The influence of one gene therefore depends upon the presence of others. But such interaction may take different forms, a well-known variant of it being provided by the *modifying factors*. These are genes which exert no known influence by themselves, so that their existence can be detected only in the presence of others whose effects they modify. Such modifying factors have been studied in great detail in other species of animals and in plants, and doubtless they are as important in man as elsewhere. Indeed general indications of their activity are common in human genetics. It is quite frequently found that a given gene produces somewhat distinct results in different individuals. Albinism, for example, is inherited as a simple recessive, but the cases may depart from the extreme, and typical, form with white hair and pink eyes. Some have pale blue eyes and pale yellowish hair. If such sub-divisions of a type appear sporadically the variations may be environmental (pp. 90-6); if, on the other hand, they are characteristic of particular families, as often in albinism, they are attributable to modifying factors.

This is bell-shaped curve such that if the ordinate is y , the abscissa is x , and the number of individuals at any point along x be the frequency (f), then $\log f$ at any distance from the centre is less than the logarithm of the frequency at the centre by a quantity proportional to x^2 .

These may be detected only by their effect on the main gene. In albinism it is probable that some at least of such genes owe their modifying action to the fact that pigment production tends towards colour-saturation, so that pale individuals are more sensitive than dark to a small increase in the total amount of pigment. Often, however no such simple interpretation is possible, and one gene may act only in the situation provided by the activity of another. Thus the symptoms of epiloia are very variable, and Gunther and Penrose (1933) showed that this is in part due to the operation of modifying factors which affect the expression of the single gene responsible for the disorder. This is usually described as a dominant though it appears to be known only from its heterozygous effect. Similarly Popenoe and Brousseau (1932) obtained evidence that modifying factors affect the manifestation of Friedreich's Ataxia, though this condition is unifactorial and recessive.

A logical extension of the concept of gene-interaction embraces an exceedingly important group of phenomena constantly encountered in the genetics of animals and plants that is to say two genes, each responsible for definite characters, may combine to produce new effects of a distinct type, not merely the average or the sum of those to which they give rise independently. It is for this reason that species-hybrids are frequently found to possess characters absent from both of the parental forms. We may take as an example the fruit fly *Drosophila melanogaster* which normally possesses red eyes. Brown and scarlet eye-colour are both recessive and due to the operation of entirely distinct genes. Yet when these are brought together in the homozygous state in the same animal, they interact to produce white eyes similar in appearance to those due to the operation of a sex linked recessive distinct from either of them. The combined effect of different genes has so far scarcely been studied in man. However the almost universal nature of the type of phenomenon here discussed, which has been demonstrated in the most diverse forms, leaves no room for doubt that a search for it would prove successful.

Attention must now be drawn to an exceedingly fundamental property of genetic actions: that single genes are responsible for multiple effects. Several examples of this have already been given incidentally but the subject is one which merits special consideration. Geneticists, whether they study human material or not, are usually concerned in following the segregation of particular genes. For this purpose it is convenient to select some obvious feature which serves to mark the presence of each: a procedure which tends to obscure the multiple nature of genic action. So much so, that the mistake is sometimes made of regarding each gene as the heritable precursor of one particular character. No view could be more false. We will at present restrict our selves to discussing that aspect of it which so wrongly associates unit genes with single characters.

Quite possibly careful examination would reveal that all genes produce multiple effects, often of surprisingly diverse kinds. Even with our present limited knowledge of human genetics, the instances in which these have been detected in man are very numerous, and a few only will suffice as examples. A single gene, described as a dominant is responsible both for bone-fragility and the production of blue sclerotics; while a single recessive gives rise to the Laurence-Moon-Biedl syndrome, the features of which are polydactyly, retinal degeneration, mental deficiency, obesity and hypogenitalism. It has already been mentioned that the form of retinitis pigmentosa due to an autosomal recessive is associated with deafness, in addition to the migration of pigment into the retina (p. 48).

It is an important fact that genes may influence the general constitution to a degree quite out of proportion to their visible effects, and in a manner wholly unrelated to them. For example, albinos are, on the average, shorter in stature and less hardy than are normally pigmented persons. The presence of the gene responsible for epiloia is most easily recognized by the characteristic distribution of the adenoma sebaceum on the face, especially along the naso-labial folds, to which it gives rise. But this symptom bears no obvious

relation to the mental deficiency and production of nodules of neuroglial overgrowth in the brain, which make the prognosis of this condition so gloomy. Similarly nearly all of the genes which have arisen by mutation during the course of genetic experiments are disadvantageous in their effects, though the observable characters to which they give rise are often quite trivial. In *Drosophila*, for example, such genes usually reduce the length of life, and the number of eggs laid per day by the female; yet we may recognise them by the absence of a bristle on the thorax or by a barely detectable change in eye-colour. Nevertheless, their effect on viability makes it clear that such genes produce other and more profound changes of a physiological kind. The almost universal nature of such alterations in the general vitality of the organism assures us that the action of single genes must in general be multiple.

The facts so far described lead to a conclusion of much consequence. Genes gives rise to multiple effects, and they interact with one another to produce the characters for which they are responsible. Therefore, they must combine to form a balanced system, or *gene-complex*, constituting a form of internal environment within which each gene must act. That is to say it is not possible to alter any single gene (by recombination or mutation) without influencing the operation of many others. Similarly the effects of a given gene will be changed when it is placed in a gene-complex whose composition differs considerably from that to which it is accustomed. This situation is, of course, attained when a marriage occurs between races which rarely interbreed, so that a different genetic situation has been built up within each. The effect will evidently be greater the wider the crosses that we study: those between races, species, and genera producing progressively noteworthy results. The degree to which we can examine the activity of particular genes in different gene-complexes is, however strictly limited. Offspring can only arise from meetings between fairly closely related genera, and these must have the great bulk of their genes in common. Further in wide out-crosses the hybrids are usually sterile,

and in them each gene is still immersed in a gene-complex to half of which it has been adjusted. None the less, the effects to which a given gene may give rise when placed in a new setting may be dissimilar enough from those which we normally attribute to it. We may take a significant example from the genetics of fish. In the Mexican Top-minnow (*Platyposchus*) a single sex-linked gene *Sp* merely produces dominant black spotting. The hybrids between this and the sword-tail, a member of another genus (*Xiphophorus*), are quite healthy unless they receive the gene *Sp* from their *Platyposchus* parent, which in the hybrid gene-complex gives rise to a fatal cancerous growth (Koewig, 1929a and b).

The forms of mankind surviving to-day belong to a single species only nor do the various human races differ sufficiently to produce any detectable degree of sterility or sexual abnormality on inter-crossing and these are the first recognizable signs of those differences which lead to the evolution of races into distinct species. Consequently the amount of modification of the gene-complex which can arise from any racial crossing in man is small compared with that which can be witnessed in wide out-crossings in other animals and plants. Yet we may be confident that further study of human genetics will show clearly enough the influence upon the effect of particular genes which results from their action in somewhat distinct gene-complexes. Nor are instances of the kind unknown to-day. The woolly hair of the negro behaves as a dominant to the non-woolly type, but its heterozygous expression is subject to considerable variation in crosses with Europeans. Otto Mohr (1933) analysed an instance in which this gene (or, less probably one producing similar results) arose by mutation in a pure Norwegian stock. Here the heterozygotes were very constant. The difference in modifiability in the effect of the gene may very reasonably be attributed to the greater variability of the gene-complex among the offspring of inter-racial crosses than can arise from marriages within the same race.

Numerous instances exist in the records of experimental Genetics in which a gene, after giving new effects in a

gene-complex to which it is unaccustomed, has been restored to that from which it came (Ford 1940e). In these circumstances, it has produced once more the characters for which it is normally responsible. That is to say such an alteration in effect is due not to a change in the gene itself but to a change in the response of the organism to that gene, consequent upon recombinations in the set of genetic factors with which it has to co-operate.

A well known instance of the fact that the genes produce different effects in different internal environments is provided by *sex-controlled inheritance*¹. This is a condition in which the action of a gene is only (or more frequently) detectable in the environment provided by one of the sexes. It is carefully to be distinguished from sex-linked inheritance (p. 89) in which the relation between genetics and sex is of a mechanical kind, some genes being carried in the sex-chromosomes, which are responsible for sex-determination. Sex-controlled genes may be carried in any chromosome and when, as is usual, they are autosomal, they are transmitted equally by either sex. Their relation to sex is therefore a physiological one.

Many totally sex-controlled genes are known in lower animals. These give ordinary segregation but in one sex only though showing autosomal transmission in both. Dominant white-forelock provides a human instance, in which the character is limited to the male, so does premature baldness (p. 150) (Cockayne 1938). Incomplete sex-control is frequent in Man. A form of oligophrenia, and the Laurence-Moon Biedl syndrome are each simple autosomal recessives, but they are commoner in males than in females because the genes determining them do not always produce their effects in the environment provided by the female sex (Calk and Mather 1933). Oligophrenia occurs about twice as often in males as in females, while in the Laurence-Moon-Biedl syndrome the difference is rather less. It should also be observed that the secondary and accessory characters, whose development must be genetically determined, provide

¹ This is sometimes called *sex-limited inheritance* but that term should be avoided as it is too easily confused with sex-linkage.

examples of sex-controlled inheritance, for they appear only in one of the two sexes.

II. DOMINANCE MODIFICATION

It will now be clear that the effects of a gene can be varied by changes in the rest of the heredity material and, consequently that they are susceptible of selection. Indeed the conclusion that selection can modify the action of a gene, while the gene itself remains unchanged, is one of the highest evolutionary consequence. If the characters produced by a gene are advantageous, they can be improved, if disadvantageous, they can be minimized. Such effects have now repeatedly been obtained experimentally (p. 89).

One of the most valuable aspects of this mechanism is that which relates to the evolution of dominance. The possibilities arising from the selective modification of the effects of genes were first fully appreciated by R. A. Fisher and it is to his brilliant analysis of them that the concept of dominance modification is due (Fisher 1928, 1931). This subject must first be studied briefly from a general point of view when its bearing upon the problems of human genetics can be indicated.

The effects of rare genes are almost wholly limited to the heterozygous phase. This is indeed obvious, since the chances of bringing together two rare heterozygotes, from which occurrence alone a homozygote can arise, must be remote (the actual proportions will be discussed on pp. 120-1). Disadvantageous genes are constantly subject to counter selection, so that they must be rare, judged by their frequency in the population at any one time. Nevertheless, the organism must have a wide past experience of them since, as already explained in Chapter III, mutation is a recurrent phenomenon. Therefore, unless such genes are so lethal that their bearers leave no descendants, animals and plants will have some opportunity of modifying their response to them by adjustments of the gene-complex. Such a process will be in the direction of mitigating the influence of disadvantageous genes when in the heterozygous state; any similar adjustment in respect of the homozygote will be relatively minute,

owing to its immensely greater rarity. Therefore there will be a constant tendency for selection to modify the effects of disadvantageous genes in the direction of suppressing them in the heterozygote; that is to say to make them recessive. The converse tendency will, of course, operate upon the effects of an advantageous gene. These will be magnified in the heterozygote so that they will become dominant in expression. Furthermore, the frequency of such a gene will increase, so providing more material on which selection can act. Consequently the process will be far swifter than the drift towards recessiveness of disadvantageous characters, which depend for their maintenance upon recurrent mutation.

It is plain then that a new advantageous gene will spread through the population, while its effects will acquire dominance. That is to say it will dispossess its former wild-type allelomorph, which will become a rare recessive. Yet the spread of an advantageous gene is sometimes arrested during its course. This occurs when the characters to which it gives rise reach an optimum frequency in the population owing to a balance of selective agencies. The resulting situation is of great practical importance in medical genetics; it will form the subject of the next chapter.

When a character is so disadvantageous that the individuals possessing it contribute little or nothing to posterity it is apparent that no opportunity for dominance modification arises. In these circumstances, the original condition should be preserved, and we may expect this to be such that two doses of a gene produce a greater effect than one. It is found, indeed, that moderately disadvantageous genes are recessive. Yet a class of genes also exists responsible for extremely disadvantageous effects when heterozygous; while the corresponding homozygotes, if obtainable, produce even more serious results so that, in many instances, they do not survive. These are obviously the group in which dominance modification has never taken place. Nor has it in respect of the rare members of a multiple allelomorph series, for these will hardly ever be brought together save in experimental work designed to that end. We find

therefore that the heterozygotes between any two rare members of the series are intermediate, while those between each of them and the normal allelomorph are not.

These facts throw much light on genetic action in man. Many of the rare disorders are true recessives. It is noteworthy however that this state has not been perfectly attained in some of the more dangerous of them, xeroderma pigmentosum for example (p. 40). On the other hand a large number of conditions, some of a serious kind, are described as 'dominants'; epila and Huntington's Chorea may be cited from among them. Yet I have pointed out that this is an assumption in nearly every instance, since the corresponding homozygotes have rarely been studied. The theoretical considerations just outlined suggest that the heterozygous effects of such genes will usually be somewhat intermediate. Some evidence for this conclusion can be obtained in more than one way. First, a very few instances are recorded in which the homozygotes may actually have been observed, and they appear usually to produce the known characters of the condition in a highly exaggerated form. Fraser Roberts (1940) draws attention to a pedigree of a form of 'dominant' brachydactyly in which the only abnormality consists in a shortening of the middle phalanges of the index fingers and toes. An affected individual, being as usual a heterozygote, married his first cousin, the daughter of an affected man. She had probably been affected, though she was dead when the family history was compiled and the point could not be established. The couple had two children. The elder was affected to the same degree as other members of the family and proved to be a heterozygote (having one abnormal and two normal children). The younger child, however was grossly abnormal. She had no fingers or toes and her 'whole osseous system was in disorder'. She died within a year being unable to develop. She was probably a homozygote. Such a condition as this cannot be ranked as a dominant at all.

Further evidence that dangerous disabilities are rarely true dominants is supplied by the variability of their

heterozygous expression. This is notable in both the instances just cited, *epiloia* and Huntington's Chorea.

There is indeed a general tendency for the expression of a gene to be more variable when heterozygous than when homozygous. Fraser Roberts (1940) has stressed that recessive conditions in man are more constant than are heterozygous ones. Indeed I have myself found, in the course of experiments on artificial dominance modification, that the heterozygotes produce a greater range of variability and are more modifiable by selection, than are either of the homozygotes; while of these, the normal is more constant than the mutant (Ford, 1940c). The reasons for this can be stated briefly. There will often be circumstances limiting the possible range of expression of a gene. For instance, increasing amounts of a pigment tend towards saturation in their effect, while the size of an organ cannot indefinitely be increased. This should make the effect of the single-dose condition more susceptible to extraneous influences, whether of changes in the gene-complex or of the external environment, than that due to the action of the two allelomorphs. Further the normal allelomorph will have been adjusted to produce the most favourable, and therefore rather constant, effects within the range of the internal and external environments to which it is generally exposed.

The degree to which the effects of a gene are variable is called its *expressivity*. It is this quality with which we deal, for instance, in discussing the fact that the gene producing dominant polydactyly is responsible for characters ranging from well-developed extra digits on both hands and feet to an ill-formed knob in addition to the normal fingers of perhaps a single hand.

Expressivity relates to the degree in which the characters produced by a gene are expressed. On the other hand, the frequency with which a gene produces any effect at all is called its *penetrance*. Most of the genes so far discussed have complete penetrance; they are always responsible for some effect. Occasionally however genes with heterozygous manifestation fail to produce any detectable characters. Their

penetrance is incomplete. For instance, diabetes insipidus is usually due to a single gene with heterozygous expression, a so-called dominant* (p. 17). This occasionally fails to cause the disorder, which therefore skips a generation, though it should be transmitted regularly from parent to offspring. Medical practitioners must be especially cautious in advising their patients on the probability of transmitting such genes. With heterozygous expression and full penetrance, unaffected individuals cannot have affected children; but when penetrance is incomplete, occasional exceptions will occur. Should the penetrance of a gene be slight, the condition to which it gives rise will appear sporadically in certain families. In these circumstances, extraneous agencies will often tend to evoke it. There is some evidence that diabetes mellitus is due to a gene with heterozygous expression and about 10 per cent of penetrance.

It has already been pointed out that the effects of homozygotes are usually less variable than are those of heterozygotes; indeed, failures in penetrance do not seem to be encountered very often in recessives. It is possible that the Laurence-Moon Biedl syndrome, a recessive condition due to a single gene, is not always expressed, that is to say the penetrance of the gene is not quite complete.

It is, however, clear that the dominance relationships of inherited characters in man are distinctly abnormal. Nor is this to be wondered at considering that they are produced by selection, for the conditions of human society during at least the last two hundred generations have departed widely from those of all wild species. They have in fact been unique, but they have somewhat resembled the situation to which domesticated forms are subject. Even in a primitive human society individuals must have been valued for and protected by qualities other than bodily adaptations to their environment. Indeed from an early period in the evolution of Man, individuals who would have been eliminated from the populations as breeding-units during the pre-human stage must have made considerable contributions to posterity. Such a negation, or in some

Instances a reversal, of selection will not only fail to produce the normal selective modification leading to dominance, but may break down dominance relationships previously attained. It is in domesticated species that we find the greatest abnormalities in dominance adjustment: a viable dominant black form occurs in the guinea pig, while the hornless condition in cattle is nearly dominant also. Species whose domestication has been of an unusual kind are those whose dominance adjustment is particularly abnormal. Indeed the peculiarities of domestic poultry in this respect, which at first appeared mere exceptions to Fisher's theory of dominance, have provided by their very irregularities clear proof of its operation (Fisher 1935 1938). So too Man, whose exposure to selection must evidently be exceptional both in degree and in kind, supplies examples in unusual numbers of a rare condition, that of genes producing heterozygous effects which must be deleterious, but to a slight extent only. It has already been explained that this situation is not normally to be anticipated. Instances are provided by phalangeal synostosis, piebald spotting, congenital cataract, and others.

H. A. Fisher was the first to suggest that dominance is produced by selection (1928), and he concluded that this operates upon the gene-complex in the manner already described. Haldane (1930) subsequently proposed an alternative method of dominance modification. He pointed out that genes probably act by producing enzymes, and that these will operate effectively only up to a saturation level, above which further enzyme productions will produce no detectable effect. It has already been pointed out that multiple allelomorphs control a given set of characters quantitatively. Now assuming that a multiple allelomorph series exists at each locus, Haldane pointed out that dominance modification might arise by selection of different allelomorphic genes in the following way. We may suppose that the homozygote is due to the operation of unnecessarily high members of the series, since selection will favour those allelomorphs whose activity

is sufficient to raise enzyme production to the saturation level even in single dose. Rare genes will always be judged by their reaction as heterozygotes, and those will be favoured which even in that phase do not lower enzyme production below the normal saturation level, so as to evoke an imperfect development of the characters concerned. That is to say Haldane envisages dominance arising through a change in the gene itself, through selection of one rather than of another member of a multiple allelomorph series.

It may however be questioned how far multiple allelomorphs are available for this purpose at each locus. Furthermore, the level of the threshold value up to which an enzyme acts will be determined by the general constitution of the organism and so, in part, by other genes; thus it will be susceptible of modification by selection operating on the gene-complex in the manner proposed by Fisher. It should also be noticed that experimental proof of Fisher's method of dominance modification has now been obtained in a number of instances. It has indeed been possible under experimental conditions to select the heterozygous expression of the characters produced by a given gene until they have become nearly dominant in one line and nearly recessive in the other. In these circumstances, it has been established, by crossing with the normal form, that the gene itself has remained unaltered (Fisher, 1935, 1938, Ford, 1940).

It has been stressed that the genes of an organism act together to form a gene-complex adjusted by selection to give a favourable result. The chances therefore are exceedingly remote that purely random changes in the genes, such as arise by mutation, shall so fit in with the balanced system already in existence as to promote harmonious working. The probability is indeed almost overwhelming that the effects of mutations will be disadvantageous, a circumstance to which attention has already been directed. The consideration that mutation is a recurrent phenomenon also contributes to this result. Were organisms living in a constant environment it would seem almost incredible that mutations having advantageous effects should ever now arise. All that

instances a reversal, of selection will not only fail to produce the normal selective modification leading to dominance, but may break down dominance relationships previously attained. It is in domesticated species that we find the greatest abnormalities in dominance adjustments: a viable dominant black form occurs in the guinea pig, while the hornless condition in cattle is nearly dominant also. Species whose domestication has been of an unusual kind are those whose dominance adjustment is particularly abnormal. Indeed the peculiarities of domestic poultry in this respect, which at first appeared mere exceptions to Fisher's theory of dominance, have provided by their very irregularities clear proof of its operation (Fisher 1925, 1938). So too Man, whose exposure to selection must evidently be exceptional both in degree and in kind, supplies examples in unusual numbers of a rare condition: that of genes producing heterozygous effects which must be deleterious, but to a slight extent only. It has already been explained that this situation is not normally to be anticipated. Instances are provided by phalangeal synostosis, piebald spotting, congenital cataract, and others.

R. A. Fisher was the first to suggest that dominance is produced by selection (1928), and he concluded that this operates upon the gene-complex in the manner already described. Haldane (1930) subsequently proposed an alternative method of dominance modification. He pointed out that genes probably act by producing enzymes, and that these will operate effectively only up to a saturation level, above which further enzyme productions will produce no detectable effect. It has already been pointed out that multiple allelomorphs control a given set of characters quantitatively. Now assuming that a multiple allelomorph series exists at each locus, Haldane pointed out that dominance modification might arise by selection of different allelomorphic genes in the following way. We may suppose that the homozygote is due to the operation of unnecessarily high members of the series, since selection will favour those allelomorphs whose activity

phenyl-thio-urea are phenotypically similar for this character but if their constitution is *TT* and *Tt* respectively they are genotypically different. On the other hand, two individuals may be genotypically similar but phenotypically different, owing to the operation of environmental variation, and it is this phenomenon which we must now briefly study.

The environment is, in all organisms, as important as heredity in producing the characters of the individual but, as already pointed out (pp. 74-5), environmental variation is particularly difficult to examine in the Mammalia, since they are protected against it to a high degree. The reason for such protection is not difficult to find. Every organism must have an optimum environment, one which suits it best. Obviously it is to the advantage of all individuals to live as near to their optimum conditions as possible. This they may do by migration, by adjusting their habits and ecology to changing conditions, or by manufacturing as far as they can an environment of their own which they carry with them and in which they permanently live. This latter technique has been perfected by the Mammalia in a remarkable way. In lower forms it is possible to study the bodily effects of altering the more obvious components of the environment, such as temperature and humidity. Yet the thermostatic regulation of the Mammalia is such that a departure of even a few degrees from their optimum temperature, which they themselves maintain, is fatal to them. Similarly changes in humidity can have but a limited effect upon them, while the constitution of their body-fluids is regulated with great exactitude. It is plain then that Mammals live in an extremely constant environment, one which approximates to their optimum, so that they are only subject to environmental variation to a very small extent.

We are provided in lower forms with innumerable examples of the fact that the genes produce different effects in different environments, so that there is little chance of falling into the fallacy of regarding them as the inherited basis of particular characters. In Mammals, where the amount of environmental variation is so much less, this mistake is more

readily made. It can easily be shown in the majority of organisms that changes in temperature, in humidity or in other elements of the external environment, will modify the action of the genes. Yet there are instances in which such effects can be detected within the small environmental range which the Mammals can experience. This is true even for a condition controlled so accurately as temperature. The point is sufficiently striking to merit a brief description.

The Himalayan rabbit is a white form with blackish extremities. It is inherited as a simple recessive, being due to the operation of a gene c^h which is a member of the albino series of multiple allelomorphs (pp. 80-1). Himalayan rabbits are born wholly white, since the gene is one which prevents pigment formation at the mammalian constant temperature. A few degrees lower however its action is quite different and leads to melanin production. Consequently the extremities darken, for they lose heat more rapidly than the rest of the body and fail to attain the true body temperature. Thus the exposed parts, the tip of the nose, ears, tail, and the feet are blackish in adult Himalayan rabbits. It can be shown experimentally that the Himalayan character is not due to the operation of a gene controlling pattern, but to one which produces different effects at different temperatures. If an area on the back of Himalayan rabbits be shaved, the hair which grows again will be white if the animal be kept warm and black if it has been kept in very cold conditions. Several other genes interacting with temperature in a similar way have been studied in the Mammalia. Examples are provided by those responsible for two of the three chinchilla phases in the rabbit, and for the Siamese cat.

No such striking environmental effects have so far been detected in Man, and our knowledge of environmental variation in human genetics is small. It must be sought rather in less obvious directions. One of these is the effect of maternal age upon the penetrance of the genes possessed by the offspring. It is thought that a number of conditions, some of them in part genetic, are expressed with greater frequency in children as maternal age advances. An instance

of these is mongolian idiocy (Penrose, 1933). This is a very serious condition, often causing death. It is believed to be inherited, possibly it is a dominant with incomplete penetrance. However this is not certain, for the occurrence of environmental variation introduces special difficulties into the genetic analysis.

Examples of the phenomena now under discussion are evidently provided by those genes whose known effect is limited to increasing the susceptibility of a patient to infection or to other conditions. There can be no doubt that the liability to develop cancer is inherited. Haldane (1938) shows that the chances of cancer appearing in an individual are very much greater if one of his parents has suffered from the disease than they are among the members of a comparable random sample of the population. It is undoubtedly true that one of the chief agents in the production of cancer is long-continued irritation at a point. But the probability that such irritation shall initiate a cancerous change is greater in some constitutions than in others and it is this tendency which is, at least in part, inherited. One of the most baffling features of cancer is the multiplicity of its forms. It is possible, indeed, that some of these may be very dissimilar in most respects produced perhaps by different exciting agencies acting in distinct genetic situations. This may well be true of the carcinomata and the sarcomata.

It is easy to break down an adjustment, and in a variety of ways, though it may be hard to build it up. Conceivably a cell may dedifferentiate through many causes, nor can somatic mutation be eliminated from among them. Were cancer initiated by one specific mutant change, the low level of mutation-rates would reduce this factor to nearly negligible proportions; but a number of distinct mutations may well evoke a cancer. Even so, I am not inclined to attribute much importance to mutation in the production of cancer.

Out of 953 sons whose fathers had died of cancer, 14 had developed that disease. In a random sample of 93,300 men and boys of corresponding ages, only 85 on the average develop cancer instead of the 1,400 expected if the frequency were the same as in the first group. Such difference cannot be ascribed to chance.

Cases are sometimes encountered in which a melanotic tumour gives rise to secondary growths one or more of which are unpigmented. These suggest independent mutations. It is much more probable, however that they have spread as metastases from the original site. If so, they represent environmental modifications, the growth taking different forms in different parts of the body. Indeed the hereditary tendency in cancer is somewhat opposed to the hypothesis that somatic mutation is a usual cause of the disease. Though genes certainly exist which raise the mutation-rate, it is unlikely that they would account for an hereditary effect of the observed magnitude.

The genetic components in the control of cancer may well be complex and various. Their nature is quite unknown, though there can be no doubt of their existence. The diversity of the disease in Man warns us that this may be yet greater between different groups of organisms, so that attempts to deduce the genetics of human cancer from breeding experiments in animals should be made with extreme caution.

The influence of the environment in evoking the effects of genes is apparent in a number of other diseases. As is well known, rickets is due to a deficiency of vitamin D. This may arise from an insufficiency of those articles of diet containing it, such as fish-oil, eggs, butter milk, and cheese, or under-exposure to sunshine; for ultra violet light leads to the production of vitamin D in the skin from pro-vitamins such as ergosterol. The disease is common among children of the poorer classes brought up in the sunless conditions of big cities. But it arises so much more easily in some constitutions than in others that before the discovery of vitamins it was classified simply as an inherited defect. Among slum populations exposed to an apparently similar environment, it will occur frequently in some families but not at all in others, while children who develop rickets may have healthy brothers or sisters, though there may be no obvious difference in their upbringing. There is in fact fairly strong evidence that, in some cases at least, susceptibility

to the condition is due to the action of a single gene with heterozygous expression. When both vitamin D and a sufficiency of sunshine are lacking, this would ensure the inheritance of rickets upon simple Mendelian lines, though the segregation of the gene would be completely obscured in a family supplied with a well balanced diet. This is clearly a parallel situation to that described in Chapter I, in which the production of yellow fat in rabbits is uni-factorial and recessive, giving rise to strict Mendelian segregation but only in animals supplied with green food. Without this article of diet, the presence of the gene is undetectable.

The allergies are due to various environmental stimuli operating in the presence of a single gene, usually described as an autosomal dominant. However Wiener *et al.* (1936) have demonstrated that it produces allergy developing before puberty when homozygous, and allergy developing after puberty or else normal carriers when heterozygous. It is partially sex-controlled, since about twice as many males as females are affected; the sexual difference presumably being restricted to the heterozygotes. Allergic disease may assume numerous forms: infantile eczema, Besnier's prurigo, lichen urticatus, urticaria, light or cold-sensitized skin, food-allergy asthma, hay fever, migraine, and others; including angioneurotic oedema, of which a distinct non allergic form also exists, inherited as a simple dominant. Sometimes, however, given form of allergy is inherited in a family or in a small group within a family in which various types appear. Actually a single gene is responsible for all, but other genes determine which tissues are particularly liable to become sensitized in its presence.

As already mentioned, susceptibility to infectious disease is often inherited (see also p. 134). Gruneberg (1903) showed that a single gene with heterozygous expression is responsible for an inflammatory condition of the accessory nasal passages. The penetrance of the gene is incomplete since its action depends upon exposure to infection. It can often be said in general terms that some constitutions are more susceptible to infection than others, though the genetic contribution is

may be entirely unknown. Doubtless it must often be multi-factorial. When twins are born of a syphilitic mother instances are known in which one only has contracted the disease, though their opportunities for infection must have been equal and great. Such a difference as this must almost certainly be genetic.

The genetic influence in infectious disease is of course more difficult to assess with advancing age, since the hereditary constitution becomes one only out of many agents predisposing to immunity or the reverse. The medical history of each individual and his past and present habits of life, in addition to his genetic outfit, are of great and obvious importance in determining resistance to infection.

IV GENETIC PHYSIOLOGY IN MAN

The methods by which genes produce the characters for which they are responsible have been studied in much detail in lower forms (Goldschmidt, 1938). Very little information on this subject is so far available in Man. Nevertheless, it would well repay careful investigation, although certain aspects of it requiring experimental analysis are inappropriate to human material.

It has been established (Ford and Huxley 1937) that genes control rates of processes in the body and the time of their onset. There can be no doubt of the general importance of this concept, and its application to Man may briefly be considered.

No reference has so far been made to eye-colour although it is one of the more obvious of human characters. I have avoided the subject on account of the unsatisfactory state of our knowledge respecting its genetic control. The view has long been held that the distinction between the presence of brown pigment in the eye and its absence, which gives rise to the blue or grey shades, is uni-factorial, brown being dominant. This appears to be correct, but it is an undoubted over-simplification. There is a prospect, however that the subject will be greatly advanced in the near future. The point to which special attention must be drawn is the

circumstance that all human eyes save the extreme albino (in which black pigment is absent from the tapetum) are blue, due to a scattering of light by connective-tissue, unless brown pigment is deposited in the iris. However when this occurs it does not take place until after birth, so that the eyes of infants are usually blue, whether they are destined to remain so or not. It appears highly probable, moreover that variations in the rate of deposition of the brown pigment and the time of its appearance are responsible for some of the difference in human eye-colour and that these are genetically controlled.

It is a striking fact that the newly born human baby possesses certain features usually found only in the foetus of other mammals; the cranial flexure, for instance. This circumstance has been somewhat over-stressed by Bolk (1926), who held that a process of foetalisation has largely been responsible for human evolution. This seems to be an exaggeration, yet it is clear that an alteration in timing, such as the delay in closure of the cranial sutures and the general lengthening of the baby phase, has played an important part in the establishment of the definitely human characters. Doubtless they have been produced by selection favouring genes which slow down rates of development. Variations in rates of growth and development are often to be observed among embryos, even in the remarkably constant environment of the mammalian uterus. These must be largely genetic, and represent the type of variation available for such selection.

Some information exists upon the manner in which a few of the human genes produce their effects. A single factor recessive in operation, prevents the formation of an enzyme enabling Man to oxidise homogentisic acid (a substance formed in the break down of tyrosine and phenylalanine). This intermediate product therefore appears in the urine, which darkens on standing. The defect is known as alkaptonuria. It tends to produce arthritis, and usually leads to a blackening of the bones and cartilages (Hogben, Warrall, and Zieve, 1933). The abnormality just described may be

compared with phenylketonuria, in which a single factor produces a recessive metabolic disorder leading to the excretion of phenylpyruvic acid in the urine. The same gene is responsible also for what appears to be a very distinct effect, since phenylketonuria patients are, in addition, mental defectives of low grade.

Finally it will be instructive to draw attention to a condition which can arise either genetically or environmentally. This is diabetes insipidus, the chief symptoms of which are intense thirst and polyuria. It is due to a single factor heterozygous in expression, which interferes with the action of the posterior lobe of the pituitary body. Of this, the disease is the direct consequence; so much so, that it can be produced also by a lesion of the posterior lobe of the pituitary resulting from syphilitic meningitis or other causes. In such a situation as this, the interaction of heredity and environment is rather clearly revealed. It will be apparent, indeed, that genes affecting the operation of the endocrine organs may be responsible for important and widespread effects in the body. Others have not so far been analysed in Man, but they are known elsewhere in the Mammalia. Thus a gene is responsible for recessive dwarfing in mice owing to its action on the anterior lobe of the pituitary which is demonstrably defective. Pituitary grafts allow such dwarfs to attain nearly to full size.

Studies on genetic physiology and on the interaction between heredity and environment, in the widest sense, are greatly needed in Man. With all its limitations, the subject could be considerably advanced even in the present state of our knowledge. It is one to which the attention of those interested in human genetics should especially be directed.

CHAPTER V

POLYMORPHISM

I. INTRODUCTION

POLYMORPHISM IS A condition of exceptional interest and importance. It may be defined as the occurrence together in the same habitat of two or more forms of a species in such proportions that the rarest of them cannot be maintained by recurrent mutation (Ford, 1940a). It will be helpful to explain and expand this definition, and then to consider its implications in some detail. In its earlier stages this account may appear but little related to the practical needs of human genetics. It will later become apparent that this impression is erroneous. Some knowledge of the theory of polymorphism is invaluable for a clear understanding of the blood groups and kindred phenomena. It will be seen, moreover that such theoretical analysis provides the only basis on which certain conclusions of importance can be reached.

Any species may assume distinct forms in different regions, as the white, the mongolian, and the negroid races of man. This is geographical variation. It is not an example of polymorphism, the definition of which is so framed as to exclude it. Only when the forms in question persist together in the same habitat as clear-cut entities can it be said that a polymorphism is established. But this must be distinguished from the occasional segregation of genes having disadvantageous effects. These are eliminated by selection and, consequently are maintained in the population only by rare recurrent mutation. Furthermore, it can be shown that the spread of genes giving rise even to minute disadvantages will be checked at an early stage (Fisher, 1930a).

As well as such unfavourable genes, it is necessary also to consider those which are neutral as regards survival value. However Fisher (1930b) has demonstrated that, in order

to produce effective neutrality of this kind, the balance of advantages between contrasted allelomorphs must be extraordinarily exact, so that such genes must be very rare. In addition, without the help of selection their spread through the population is exceedingly slow. Indeed the number of individuals which possess a gene of approximately neutral survival value cannot greatly exceed the number of generations since its occurrence, if it be derived from a single mutation (Fisher 1930a). Furthermore, with particulate inheritance, mutation is so rare (pp. 61-3) that its recurrent nature cannot hasten the process very materially. Therefore the spread of such genes will often require a period of time so vast as to fall outside the scale at least of minor evolutionary trends.

We are not here concerned with environmental variation. Setting this aside, and bearing in mind the considerations just outlined, we may be fairly confident that when a form occupies even two or three per cent only of a given population it will probably possess some advantage. In these circumstances, it may either be in actual process of spreading, or else it may be maintained in a constant proportion by a balance of selective agencies.

These two alternatives, respectively named *transient* and *balanced polymorphism* (Ford, 1940a) each represent conditions of outstanding interest. In the transient type, a form previously rare spreads through the population, which becomes polymorphic during the process. Such an occurrence is perhaps always due to a change in the environment, which gives some value to a character previously disadvantageous. Formerly this was not ranked as polymorphism at all, for the term was reserved for the distinct class of phenomena in which stable ratios are involved. The frequent difficulty of deciding in what instances stability is in fact attained has made the inclusion of the transient situation a practical necessity. To take an example: black forms of many species of moths have appeared in manufacturing districts and have largely supplanted the normal pale types there during the last fifty or sixty years (see Ford, 1937). While this change

was in progress, these populations were in a state of transient polymorphism.

True, or balanced, polymorphism always involves an equilibrium between opposed selective agencies. As already pointed out, a form will usually possess some advantage if it has spread through a population to any considerable extent. But normally this will lead merely to a transient polymorphism. Stability will be attained only when the advantage conferred diminishes, and is finally converted into a disadvantage, as the form becomes proportionately commoner. Such a check to the progress of an initially advantageous gene may or may not be genetic. It will be imposed automatically if the heterozygote is at a greater advantage than either of the two homozygous classes. But there are instances in which it is actually undesirable that the forms in a given heterogeneous population should depart from definite proportions, which constitute their optimum. Thus the existence of the two sexes is a situation which falls within the definition of a balanced polymorphism. In each species they are maintained at an optimum ratio which is generally near equality. We may be confident that any modification of the sex-determining mechanism tending to increase the frequency of one sex at the expense of the other would be opposed by selection.

Other, and remarkable, instances of polymorphism in man occur in addition to sex. These must now be considered.

II. THE TASTE TEST

The ability to taste phenyl thio-urea in low concentrations has already been discussed as a simple example of the working of Mendel's first law (pp 9-15). It will be recalled that those who can detect this substance possess a gene *T* dominant in effect, while the inability to do so is recessive and due to the operation of an allelomorphous pair *t*. When both parents are non-tasters, so are all their children.

'Tasters' can detect it in aqueous solutions of 50 parts per million while 'non-tasters' cannot. Both types can usually do so in concentrations of 400 parts per million.

to produce effective neutrality of this kind, the balance of advantages between contrasted allelomorphs must be extraordinarily exact, so that such genes must be very rare. In addition, without the help of selection their spread through the population is exceedingly slow. Indeed the number of individuals which possess a gene of approximately neutral survival value cannot greatly exceed the number of generations since its occurrence, if it be derived from a single mutation (Fisher 1930a). Furthermore, with particulate inheritance, mutation is so rare (pp. 61-3) that its recurrent nature cannot hasten the process very materially. Therefore the spread of such genes will often require a period of time so vast as to fall outside the scale at least of minor evolutionary trends.

We are not here concerned with environmental variation. Setting this aside, and bearing in mind the considerations just outlined, we may be fairly confident that when a form occupies even two or three per cent only of a given population it will probably possess some advantage. In these circumstances, it may either be in actual process of spreading, or else it may be maintained in a constant proportion by a balance of selective agencies.

These two alternatives, respectively named *transient* and *balanced polymorphism* (Ford, 1940a), each represent conditions of outstanding interest. In the transient type, a form previously rare spreads through the population, which becomes polymorphic during the process. Such an occurrence is perhaps always due to a change in the environment, which gives some value to a character previously disadvantageous. Formerly this was not ranked as polymorphism at all, for the term was reserved for the distinct class of phenomena in which stable ratios are involved. The frequent difficulty of deciding in what instances stability is in fact attained has made the inclusion of the transient situation a practical necessity. To take an example: black forms of many species of moths have appeared in manufacturing districts and have largely supplanted the normal pale types there during the last fifty or sixty years (see Ford, 1937). While this change

reality of such polymorphism in man. This is of sufficient importance to merit a brief description.

It appeared just conceivable that a study of the anthropoid apes might provide decisive evidence that a long-established polymorphism is at work in maintaining at optimum proportions the genes controlling this taste effect. The possibility of such an approach was realized, and tested successfully by Fisher Ford, and Huxley (1939). They found that 'tasters' and non-tasters exist in at least two species of ape, the orang-utan and the chimpanzee. These animals can be classed for this character without risk of confusion, and their level of perception proved to be approximately the same as that of man. Using the chimpanzee, it was found that out of 37 individuals examined, 7 or 26 per cent, were non-tasters, which therefore exist in approximately the same proportion among them as in the human race. Without the condition of stable equilibrium, it is hardly conceivable that this gene-ratio should have remained the same during the million or more generations since the separation of the anthropoid and hominid stocks. We thus have evidence that over this period the heterozygotes for the evidently valueless character concerned have enjoyed a selective advantage over the two homozygotes, and this both in the lineage of the evolving chimpanzee and in that of evolving man. Wherein the advantage lies it would at present be idle to speculate, except that it is presumably of a physiological nature. However of its existence there can be no room for doubt.

III. THE BLOOD-GROUPS

(a) *The O, A B Series*

Similar in principle to the polymorphism of the taste test is that involved in the human blood-groups. These are so important that they must be discussed in some detail.

Cases frequently arise in which it is necessary to transfuse blood from one individual to another. It had long been realized that though such a procedure is sometimes highly

successful, at others it is attended with serious and often fatal consequences. The technique was therefore useless until the basis underlying such discrepancies had been analysed. This has now been done, with results which must briefly be summarized.

The red blood corpuscles sometimes contain *agglutinogens*, substances which react with others called *agglutinins* present in the plasma of another individual. When they do so, the corpuscles run together or agglutinate, so blocking the blood vessels. In transfusion, it is important not to use blood whose corpuscles will be agglutinated by the plasma of the recipient. The reverse procedure, that of injecting blood whose plasma can agglutinate the recipient's corpuscles, is generally harmless; for in these circumstances, the donor's plasma is too much diluted to produce detectable effects.

Several distinct types of *agglutinogens*, also called *antigens*, exist. The two most important are known as *A* and *B* and the corpuscles may contain both, one or the other alone, or neither of them. Individuals therefore may be placed in one of four classes, called *AB*, *A*, *B*, and *O* depending on their content of these substances. In class *AB* both *agglutinogens* are present, and in *O* both are absent. The *agglutinins* in the plasma are also of two main, and corresponding, types. These are called α and β , and they are also known as antibodies of *A* and *B*, or anti-*A* and anti-*B*. They react with *agglutinogens A* and *B* respectively. It is evident, therefore, that the corresponding *agglutinin* and *agglutinin* can never co-exist in the same individual, for this would be fatal to it. On the other hand, an *agglutinin* or an *agglutinin* is never absent from any person in whom it can safely occur. Thus those possessing *A*, *B* or *O* *agglutinogens* always carry β , α , or both *agglutinins* respectively. The same is true of the existence of *agglutinogens* in the absence of their specific *agglutinins*.

The *agglutinogens* (antigens) *A* and *B* usually occur also in various gland cells, and may appear in the secretions which these produce. Thus they are generally found in small quantities in tears and in urine, but they occur in saliva and

in semen in a much higher concentration than in blood. This is due to the action of a gene S 'dominant' in effect, which allows the secretion of these agglutinogens, while the recessive s prevents it. It seems that between 18 and 28 per cent of the population are of the latter type, in which the agglutinogens are absent from the various gland cells and their secretions.

It is clear that individuals might be classed with reference either to the agglutinogens O A B or AB in their erythrocytes, or to agglutinins α , β , or $\alpha\beta$ in their plasma. Actually it is the former plan which is adopted, and the standard nomenclature for the groups is O A , B , and AB . This is the one officially recognised by the Health Committee of the League of Nations.

Unfortunately numbers based upon two conflicting systems are sometimes employed for the blood-groups. Groups AB , A , B , and O were numbered 1 to 4 by Moes, but numbers 4 and 1 are transposed by Janaky. This has resulted in much confusion, and probably in accidents in transfusion. These numbers are not now employed in scientific publications, and they ought never to be used. They are only mentioned here because one or other of the numerical systems (that of Moes in England and sometimes of Janaky on the Continent) is still adopted by a small, and it is hoped decreasing, number of institutions.

Since any donor may be used who does not carry the agglutinogens corresponding to the agglutinins in the plasma of the recipient, the possibilities of blood transfusion can easily be determined. They are represented in Table A.

Group O forms the class known as 'universal donors' since their blood is compatible with all groups. (Table A, first horizontal line within the table). However the blood of all groups but their own is incompatible and sometimes fatal to them when they are recipients (*ibid.*, first vertical line). On the other hand, the AB group can supply blood for no group but its own (*ibid.*, lowest horizontal line), but can receive blood from any group (*ibid.*, last vertical line).

The blood-group of any individual can be determined by

peoples concerned and the populations among which they dwell and, still more important for our purpose, the stable nature of the blood group ratios within given races.

These blood-groups are controlled genetically by a system of multiple allelomorphs. Group O is due to the operation of a pair of allelomorphic genes gg recessive in effect. The groups A and B are each produced by a different gene substitution (G^1 or G^2) at the locus of g . Both the A and B groups are dominant to group O. That is to say the genotypes G^1G^1 and G^1g both give rise to group A and are not distinguishable in their effect; nor are G^2G^2 and G^2g , producing group B. However the genes G^1 and G^2 interact to produce the AB group, which, genetically is G^1G^2 . This, therefore, as group O can have but a single genotype.

It will be evident that, from the point of view of blood-grouping, the results of any marriage can be predicted within certain limits. These can readily be deduced from the information just provided, and they are listed in Table C. The importance of these facts will be discussed on pp. 115-16.

Type of Marriage	Blood-groups absent among children
O × O	A, B, AB
O × A	B, AB
O × B	A, AB
A × A	B, AB
B × B	A, AB
A × B	—
O × AB	O, AB
A × AB	O
B × AB	O
AB × AB	O

Table C. Ten types of marriage are possible with respect to the four blood-groups O, A, B and AB. These are listed in the first column. In the second column will be found the blood-groups which cannot appear among their children.

It is now possible to subdivide group A, but not group B. The reaction of agglutininogen A to agglutinin α may either be strong (group A1) or weak (group A2). The differences between them are not believed to affect the safety of blood transfusion, so that it is not usual to undertake the labour of discriminating between them in ordinary blood tests, consequently Table A has not been subdivided in respect of them. Certain indications suggest, however, that it is safer in an A to A transfusion always to use the same type of A as that possessed by the recipient.

Taylor and Prior (1938) found that in England approximately 17.0 per cent of group A belong to the A2 section. The recorded proportions in Denmark and the United States are higher being 24 and 31.5 per cent respectively while in the native population of Hawaii group A2 is said to be absent (data from Wiener 1939). In general, we may assume that about one quarter to one fifth of those possessing A are of the A2 type. Additional, and corresponding, groups A1B and A2B of course exist in similar proportions within the AB group.

Genetically groups A1 and A2 are controlled by two genes G^A and G^A allelomorphs to one another and to G^B and g . They form a multiple allelomorph series in the order G^A G^A G^B g each of which is dominant in effect to those below it. G^B however though dominant to g interacts with G^{A1} and G^A to produce groups A1B and A2B respectively. It will be apparent, therefore, that group A1 may carry genes G^{A1} or g , but not G^B in single dose; but that groups A2 and B can only carry g in addition to the apparent gene.

Remembering that not more than two of these genes can co-exist in the same individual, the genetics of the blood groups, taking into account the subdivision of A into groups A1 and A2, can easily be worked out. This refinement naturally limits still further the possible results to be obtained from marriages of the various types. Such information, additional to that provided in Table C, is given in Table D.

Marriage	Blood-groups absent among children	Marriage	Blood-groups absent among children
A1 × O	B, A1B A2B	A1B × A1	O A2
A2 × O	A1 B, A1B, A2B	A1B × A2	O A2, A1B
A1 × A1	B, A1B, A2B	A2B × A1	O
A2 × A2	A1 B, A1B, A2B	A2B × A2	O A1 A1B
A1 × A2	B, A1B, A2B	A1B × B	O A2, A2B
A1 × B	—	A2B × B	O, A1, A1B
A2 × B	A1 A1B	A1B × A1B	O A2, A2B
A1B × O	O A2, A1B, A2B	A2B × A2B	O A1 A1B
A2B × O	O A1 A1B, A2B	A1B × A2B	O, A2

Table D. Marriages involving group A, when this is subdivided into A1 and A2, and the blood-groups which cannot appear among their children.

Yet another subdivision of A, group A3, has now been detected, having a still weaker reaction with agglutinin *a* than has A2. The data of Friedenreich, one of its discoverers, suggest that rather less than 0.5 per cent of the A group belong to A3. His investigations indicate that it is inherited, and that it is probably determined by yet another substitution (G^{A3}) at the locus of g whose effect may be recessive to G^{A1} and G^{A2} and dominant to g . Presumably it interacts with G^B to produce a group A3B of great rarity. If these indications are substantiated, we have a multiple allelomorph series of five terms at the g locus: G^A G^{A1} G^{A2} G^B and g , and the genetics of A3 could be worked out on similar lines to those of the other groups. However the tentative nature of the information at present available on A3 does not make it desirable to provide tables illustrating the results of the marriages involving it. Furthermore, even if this could be done with confidence, they would be of negligible value owing to the rarity of the group.

It should be explained that the nomenclature of these and other blood-group genes adopted in the past has been

unsatisfactory. The genes for groups O, A, and B have themselves been called *O*, *A*, and *B*. This breaks the rule to be adopted in the nomenclature of multiple allelomorphs (p. 20): that the same symbol, distinguished by a suffix, should be used throughout. The allelomorphic nature of such genes is then still apparent when the signs alone are employed. The use of different letters should always indicate genes at different loci. Furthermore, to represent in the same way the genes and the blood-groups which they control invites a confusion which should never exist: that between the characters and the genes responsible for them (pp. 90-1). In addition, in reading works on blood-grouping, it is often by no means clear whether a particular letter refers to a gene or to a group. This can only be determined by a careful study of the passage concerned, and sometimes not then. Also the use of the cypher (0) for a gene, in distinction to another letter for its allelomorph, suggests absence of genic material at the locus concerned, and of this we have no evidence here.

A more intolerable practice is sometimes adopted, in which the genes for groups A and B are designated *A* and *B*, but the gene for group O is called *R* (to suggest the recessive), the genotype then being *RR*. To represent two out of three genes by the same letter as the groups they produce, and the third by a letter quite different from its group, leaving nothing to suggest allelomorphism, leads to a confusion for which there is no parallel in genetic notation. I have therefore employed the ordinary multiple allelomorph notation for the blood-group genes; using *g* (=group) for that with the recessive effect, and the capitals and suffixes for the dominants, as would be done in any other such series.

(b) *The M N Series*

In addition to the agglutinogens so far discussed, others exist in human blood which interact with agglutinins present in the plasma of various animals. Only two such series have so far been analysed: the first comprises two agglutinogens known as *M* and *N*. All human red blood

a single pair of allelomorphs without dominance, carried in a different chromosome from that containing the *g* locus. Groups M and N are homozygous, and MN is the heterozygous class. The genes involved may be represented by R^M R^N for group M and $R^M R^N$ for group N so that MN has the genotype $R^M R^N$. Here, as in the O, A, B series, I have departed from the current notation, in which the genes and the classes which they produce are represented by similar

Type of Marriage	Blood-groups absent among children
M \times M	N, MN
N \times N	M, MN
M \times N	M, N
M \times MN	N
N \times MN	M
MN \times MN	—

Table E. Marriages involving the M, N, and MN blood groups and the types which cannot appear among their children.

letters, so obscuring allelomorphism. My reasons for doing so are sufficiently explained on pp. 110-11. Consequently I have used the same letter for the two phases of the same gene, in conformity with ordinary genetic usage, R being chosen (with reference to rabbit serum). With an intermediate heterozygote it is not desirable to employ capital and small letters for the respective allelomorphic states, as these should indicate dominance. Thus, I have adopted a fixed letter with a varying suffix, which demonstrates both allelomorphism and the relation of gene to character.

It is, of course, only necessary to apply Mendel's first law to discover the result of any marriage, so far as the M, N series is concerned. However this information is provided in Table E, and its significance will be discussed on pp. 115-16.

(c) *The Rh Group* (see also p. 152)

It has recently been shown that the human red corpuscles usually contain an antigen called Rh, which reacts with immune sera prepared by injecting rabbits or guinea-pigs with the blood of rhesus monkeys (see Taylor 1948). The presence of the Rh antigen is inherited as a simple dominant. It occurs in about 85 per cent of the population (calculated on white Americans). Racial differences in frequency are, however, now known, as is the existence of more than one kind of Rh, analogous with the different forms of A.

Antibodies for Rh do not normally occur in human plasma. However when blood containing the Rh antigen is given to some of those lacking it, a slight haemolysis may result. Rh antibodies are then produced so that Rh blood given at a later transfusion may have grave results.

Serious reactions are sometimes observed in women transfused for the first time after the birth of a child (or a miscarriage). These seem to be due to immune antibodies formed in response to antigens present in the foetus but absent in the mother of these, Rh appears to be particularly important. Taylor suggests that the passage through the placenta of such maternally formed antibodies may be the cause of erythroblastosis foetalis: a haemolytic disease of the newly born.

The detection of human Rh antibodies may be difficult or impossible. Taylor therefore advises that Rh-negative blood should be used where possible, for repeated transfusions, or even for a first transfusion to a woman recently pregnant.

IV PRACTICAL APPLICATIONS

A knowledge of the O, A, B blood-group series is of course essential in the wide range of cases in which transfusion is desirable. So it is also in medico-legal work, since blood-stains can be assigned to their correct blood-groups, thus assisting in their identification. The genetic aspect of polymorphism, exemplified by the taste test and the two blood-group series, is also of importance to practitioners both for its legal and its medical significance.

It has been demonstrated in this chapter that it is possible to predict, within certain limits, the blood-groups which can appear among the children of parents whose grouping is known. This type of evidence is now admitted in legal proceedings which involve doubtful paternity and medical men may find themselves called upon to give expert evidence in such cases. The information which they will require is summarized in Tables C-E in this chapter.

Evidence of this kind may of course be required by either party in divorce and kindred proceedings. It may be shown that a child cannot be the offspring of its legal father or alternatively that a man cannot be the father of a child attributed to him. The reverse procedure, that of proving that a man must be the father of a particular child, is not feasible. For this reason, the tables are arranged to show which blood-groups cannot appear among the children of particular types of marriage, as this is the information required in practice.

In all such circumstances it will be well first to use the simple O A, B AB series, in the hope that this may provide the required data. If it does not do so, recourse can be had to the M, N, MN scoring, and finally group A should be subdivided (if present). It should be emphasized, however, that special experience is required for work on these latter groups, and this should not be undertaken except by an expert. The range of possibilities supplied by all three of these methods is considerable.

In this matter the expert witness must guard himself against an obvious criticism. He may be asked, 'Is it not true that genetic factors are subject to sudden and unpredictable changes, called mutations, and (granting this fact) is not evidence depending upon their inheritance wholly suspect? How in fact, can it be asserted in any legal case that the genetic factor in question has not changed in this way?' The information required to answer these questions has been given in Chapter III. However it may be a convenience to provide a correct reply to them here.

The hereditary mechanism of at least all higher organisms

is of the particulate or Mendelian type, which depends for its operation upon the extreme permanence of the hereditary factors themselves. Were these to change (mutate) in as many as one individual in even a few thousand, the system would break down. A study of such mutations throughout the widest selection of living organisms demonstrates that a mutation rate of 1 in 50,000 individuals is extremely high, and this frequency is hardly ever exceeded. Inheritance in man is of the same type, and these conclusions are strictly applicable to him. But we are no longer dependent upon analogy for a knowledge of human mutation-rate. It has now been possible to study this in several instances (pp. 62-3), in which it proved to be, when most frequent, of the same order of rarity as in other animals (see Haldane, 1935).

We can therefore be confident that the error introduced into blood-grouping by mutation is not greater than 1 in 50 000, and is probably less. Such minute chances are outside ordinary experience. Few legal cases can have been decided during the present century in which the possibility of mistake was not considerably greater than this. Were a chance of error far greater than that introduced into blood grouping by mutation taken into consideration in legal procedure, the law could operate no longer.

From the medical point of view the human polymorphisms, as exemplified by the taste test and the three blood-group series, are of importance from several aspects. First, they provide a means of marking chromosomes for linkage studies, the value of which is discussed on pp. 127-8. They are especially suitable for this purpose since a large proportion of the population is heterozygous for the genes controlling them. Secondly the light which they throw on paternity already exploited from the legal aspect, is of assistance in checking the validity of a pedigree in which some inherited condition appears as a rarity or is expressed in an exceptional way. In these circumstances, single cases may greatly affect the interpretation, and the possibility of doubtful paternity should be investigated carefully whenever it is suspected.

Finally we must return to the general principles outlined in the introduction to this chapter. It was there shown that the genes controlling a polymorphism will not usually be of equal survival value. The correctness of this view has now been demonstrated in respect of the taste test (p. 103), and theoretical considerations indicate that it may be equally applicable to those of the blood-group series and *S*. Here the proof is still lacking, but evidence may yet accumulate to show that the survival value of the different members of these series is not identical. Information bearing on this matter might be obtained from a study of the blood-groups of abortions, still-births, and children dying in infancy. It seems possible that the double dominant group (AB) might be unduly common among them, indicating its excess elimination. However Professor R. A. Fisher has lately suggested to me that it is not too remote a possibility to seek evidence of differential survival from a comparison of the blood-group frequencies of the young and the elderly.

We can hardly suppose that the blood-groups represent instances of transient polymorphism, rather they must be of the balanced type (p. 101), associated with ratios which have long remained stable. That the proportions of the groups should vary widely between different races does not appear to contradict this view. The genetic constitution of the more distinct of the human races must differ rather considerably providing internal environments whose optimum conditions may well be dissimilar. On the other hand, the evidence derived from gypsies and from Jews (p. 107) indicates that the blood-groups within races have attained stable proportions which must have endured for long periods of time. Furthermore, the anthropoid apes are the only mammals in which are found antigens identical with the human *A* and *B*. In this respect the lower Primates are no nearer man than are many other mammals, but in the anthropoids the groups are the same as in ourselves. It is strongly suggested therefore that this grouping is very ancient, having been evolved in the common ancestor of anthropoids and of man.

These considerations of course apply not only to the O A B series, but also to the M, N MN groups. Indeed it is established that substances serologically related to these antigens exist in the chimpanzee, but not in lower monkeys or in other mammals (Wiener 1939).

In the simple genetic situation of the M, N MN series, a stable equilibrium would be attained if the heterozygote class were at an advantage compared with either homozygote. This would lead to an excess of the MN group, though perhaps a minute one. It is noteworthy that such an excess is more frequently recorded than a deficit in those instances in which the group departs significantly from expectation¹ (Wiener 1939). This has been commented on with surprise though, in fact, it is not unreasonable to anticipate such an effect. However it is probably due to errors in technique for no such excess is apparent in the exceptionally careful studies of Taylor and Ikin (1939); though one might have expected mistakes to cancel one another out in data derived from the combined results of a number of workers. Yet it is quite possible that under-absorption, or the presence of agglutinins α and β , leading to an apparent excess of the MN class, may be more frequent faults than over-absorption, or the use of fluids of insufficient strength, tending in the other direction. Clearly the matter is one which merits investigation in the future.

The implications of the different viabilities conferred by the genes for the taste test, and possibly for the blood-groups, cannot be predicted in the present state of knowledge. It is conceivable that these genotypes may not be equally resistant to certain diseases. At any rate, the existence within the population of sections having unequal viability small and elusive though the distinctions may be, is one deserving the careful attention of medical practitioners and, perhaps, of insurance companies.

¹ The expectation is that the proportion of the heterozygote class (MN) should be equal to twice the product of the square roots of the other two classes (M and N), see p. 120.

CHAPTER VI

METHODS OF STUDY IN HUMAN GENETICS

IT WILL BE evident to those who read this book that further research on human genetics is much needed. Indeed, the subject is only just reaching the stage at which it can usefully be applied to practical problems, so that additional knowledge will now serve greatly to extend its scope. It is by the co-operation of medical men that such advances are likely to be achieved, and the main purpose of this chapter is to indicate some of the ways in which the necessary information may be obtained. Obvious restrictions are imposed upon the study of genetics in an organism such as Man, in which experiments are impossible yet certain simple methods exist which have been designed to surmount some of them, and a selection of these will now be discussed. Some advice may be helpful both on simple means of analysis and on the type of data which it is most useful to amass. However, many methods of great importance in human genetics are too technical for presentation here, and information on them should be obtained from specialist works. This refers in particular to mathematical procedure.

In addition, this chapter will throw further light on a number of genetic phenomena. Some of these have not so far been considered, while brief reference only has been made to others which can now be explained more fully.

I. ELEMENTARY QUANTITATIVE METHODS

The student of human genetics must rank mathematical analysis among the most important of his tools, but that subject is one which can hardly be undertaken in a book of this scope. Fortunately however there exists a number of works specially devoted to it from which all the information necessary can be obtained. One of these is of such exceptional importance that it must be mentioned at the outset: this is R. A. Fisher *Statistical Methods for Research Workers*

I would also strongly recommend an excellent little treatise by K. Mather *The Measurement of Linkage in Heredity*. Yet there are a few metrical considerations which are so simple and fundamental that they may briefly be discussed here. The first of these refers to the distribution of genes in a population breeding at random.

A pair of allelomorphs autosomally transmitted can exist in three genotypes: the two homozygotes and the heterozygote. With random mating, their frequencies reach stability in a single generation, so that the proportions in which they occur remain constant until disturbed either by mutation or selection. These agencies will cause the classes to assume a new equilibrium in the next generation, which will also remain in stability unless subject to extraneous modification as before.

At whatever proportion of its loci an autosomal gene may exist, the frequencies of the three classes always bear a simple relationship to one another. That is to say the number of individuals belonging to the heterozygous class (H) is twice the product of the square roots of those forming the other two classes. Thus if the number of individuals in the homozygous dominant class (D) is p^2 and in the homozygous recessive class (R) is q^2 the three genotypes, D, H, and R, are distributed in the proportion.

$$p^2 \quad 2pq \quad q^2$$

This is a consideration of much importance. If we know the proportion of recessives in the population, the fraction of the dominant phenotype which is composed of heterozygotes is directly calculable. Suppose a disease due to a simple recessive occurs on the average in one individual in ten thousand, then approximately 2 per cent of the population are heterozygotes for it! We see at once how astonishingly widespread in the human race must be the genes which give rise to recessive defects so rare that they are judged to be little more than medical curiosities. The significance of this conclusion will be discussed on p. 180.

Suppose, on the other hand, we consider a gene with

heterozygous manifestation (a so-called 'dominant'). We may well ask how often can its homozygous effect be studied? If one individual in ten thousand possesses the heterozygous character then the heterozygote is forty thousand times commoner than the 'dominant' homozygote, which therefore appears only in one individual in four hundred million. Many of the non-recessive conditions in Man are rarer than this, so that the difference in frequency between their two homozygous classes is yet more vast. It was pointed out on pp. 17 and 87 that though many of the rare conditions found in Man are described as 'dominants' this is a pure assumption in nearly every one of them. It will be evident from the gene-frequencies involved how difficult it normally is to compare them in their homozygous and heterozygous phases, and until this is done no conclusion on their dominance can be reached.

The explanation of dominance-modification developed in Chapter IV depended upon the consideration that the effect of any rare gene will almost always be judged in its heterozygous state, the frequency of the homozygote being negligible. The basis for this assertion will now be clear.

We have so far been reviewing the distribution of autosomal genes in a population mating at random. However the normal type of sex-linkage (total sex linkage in the X-chromosome) leads to a somewhat different situation. First, stability is not immediately reached after the pre-existing frequencies have been disturbed, but the proportions in subsequent generations oscillate about their new equilibrium values. Secondly no heterozygous genotype exists in the male (strictly speaking, in the heterogametic sex) since that sex possesses a single X-chromosome only. The possible genotypes of genes carried in the non-pairing region of the X-chromosomes, and their proportions, are as follows:

Males		Females		
D	R	D	H	R
p	q	P	$2pq$	q^2

I would also strongly recommend an excellent little treatise by K. Mather *The Measurement of Linkage in Heredity*. Yet there are a few metrical considerations which are so simple and fundamental that they may briefly be discussed here. The first of these refers to the distribution of genes in a population breeding at random.

A pair of allelomorphs autosomally transmitted can exist in three genotypes: the two homozygotes and the heterozygote. With random mating, their frequencies reach stability in a single generation, so that the proportions in which they occur remain constant until disturbed either by mutation or selection. These agencies will cause the classes to assume a new equilibrium in the next generation, which will also remain in stability unless subject to extraneous modification as before.

At whatever proportion of its loci an autosomal gene may exist, the frequencies of the three classes always bear a simple relationship to one another. That is to say the number of individuals belonging to the heterozygous class (H) is twice the product of the square roots of those forming the other two classes. Thus if the number of individuals in the homozygous dominant class (D) is p^2 and in the homozygous recessive class (R) is q^2 the three genotypes, D, H, and R, are distributed in the proportion.

$$\text{■ } 2pq : q$$

This is a consideration of much importance. If we know the proportion of recessives in the population, the fraction of the dominant phenotype which is composed of heterozygotes is directly calculable. Suppose a disease due to a simple recessive occurs on the average in one individual in ten thousand, then approximately 2 per cent of the population are heterozygotes for it. We see at once how astonishingly widespread in the human race must be the genes which give rise to recessive defects so rare that they are judged to be little more than medical curiosities. The significance of this conclusion will be discussed on p. 186.

Suppose, on the other hand, we consider a gene with

heterozygous manifestation (a so-called dominant'). We may well ask how often can its homozygous effect be studied? If one individual in ten thousand possesses the heterozygous character, then the heterozygote is forty thousand times commoner than the dominant' homozygote, which therefore appears only in one individual in four hundred million. Many of the non-recessive conditions in Man are rarer than this, so that the difference in frequency between their two homozygous classes is yet more vast. It was pointed out on pp. 17 and 87 that though many of the rare conditions found in Man are described as dominant' this is a pure assumption in nearly every one of them. It will be evident from the gene-frequencies involved how difficult it normally is to compare them in their homozygous and heterozygous phases, and until this is done no conclusion on their dominance can be reached.

The explanation of dominance-modification developed in Chapter IV depended upon the consideration that the effect of any rare gene will almost always be judged in its heterozygous state, the frequency of the homozygote being negligible. The basis for this assertion will now be clear.

We have so far been reviewing the distribution of autosomal genes in a population mating at random. However, the normal type of sex linkage (total sex-linkage in the X-chromosome) leads to a somewhat different situation. First, stability is not immediately reached after the pre-existing frequencies have been disturbed, but the proportions in subsequent generations oscillate about their new equilibrium values. Secondly no heterozygous genotype exists in the male (strictly speaking, in the heterogametic sex) since that sex possesses a single X-chromosome only. The possible genotypes of genes carried in the non-pairing region of the X-chromosomes, and their proportions, are as follows:

Males		Females		
D	H	D	H	R
p	q	p ²	2pq	q ²

Consequently the ratio of recessive males to recessive females is $q : q^2$ or $1 : q$. So that if one individual in ten thousand is a sex-linked recessive, affected males are five thousand times commoner than affected females. That is to say totally sex-linked recessive conditions are immensely more frequent in males than in females.

This exposes an error which I have several times encountered in medical writings. It is sometimes noticed that a recessive defect occurs rather more often in males than in females (perhaps three or four times as frequently). Realising that recessive sex linkage leads to an excess of males, it has been suggested that the gene in question is carried on the X-chromosome. With one exception of a very specialised type, this can never be true in such circumstances. The sex difference between recessives in total sex-linkage is always so great that a small excess of males, amounting to a few times the females, cannot possibly be attributed to it. Moreover a rough estimate of the frequency of the condition in the population can usually be made, allowing a comparison between expectation and realisation in the sex of affected persons.

There remains the possibility of partial sex-linkage. As pointed out on pp. 46-8, this does not produce any association with sex when the population as a whole is considered. Only within given families can such a relation be detected, and this will take the form of a small excess of affected males in one family and of affected females in another. Clearly a small excess of one sex among individuals suffering from a recessive defect must not be attributed to sex-linkage unless it relates to inheritance within a particular family; even then it can only indicate partial sex linkage.

Totally sex-linked genes dominant in expression appear to be very rare. Possibly true dominants of this kind do not exist. The presence of the two X-chromosomes in the female would allow them a greater opportunity for occurrence in that sex. If the gene were a very uncommon one, the proportion of homozygous females would be negligible, so that the frequency of affected males and females would not differ detectably from a ratio of 1 : 2.

Dominant total sex-linkage cannot give rise to an excess of affected males. Even an excess of affected females amounting to approximately double that of the affected males must be attributed to it with caution, since the condition is at any rate extremely rare. Dominant partial sex linkage could produce a slight excess of the affected in either sex so that it is unrecognizable in the population as a whole, but it can be distinguished in a study of single families.

Small excesses of one sex among affected persons, whether of dominants or of recessives, are nearly always due to the operation of sex-controlled inheritance (pp. 89-8), and at the outset this must be regarded as by far their most probable explanation. Partial sex-linkage can be distinguished from it by a reversal of the sex-distribution when different families are compared with one another. Due regard to these considerations will prevent the repetition of a mistake which has been made on a number of occasions in the past.

It is obviously necessary to estimate the error involved in any genetic calculation. The populations which we wish to study are usually so large that it is not possible to examine every one of their members. We therefore deduce their qualities from samples which we believe may be characteristic of them. Such features as the sex ratio, or the distribution of segregating classes, are directly calculable *within the sample*; but the results must then be applied to the general population from which that sample has been withdrawn. Clearly the larger the sample, the more nearly do its attributes reflect those of the whole population. On the other hand, the greater the variability of the sample, the larger it must be if it is to provide information of a given standard of accuracy. The relation which the characteristics of a sample bear to those of the whole group can be assessed by applications of the theory of error. The necessary methods for doing so are given by Fisher (1941). However a few useful calculations of this kind are so simple that they may briefly be explained here.

The probability that a given result shall be equalled or

surpassed by chance may in appropriate circumstances, be determined by calculating a quantity called the *Standard Error* (). The frequency with which a variation as large as the standard error (or its multiple) may occur by chance is approximately as follows:

Standard Error (σ)	Probability of σ being reached by chance
$1 \times \sigma$	1 in 3
$2 \times \sigma$	1 in 23
$3 \times \sigma$	1 in 370

It is a convention to consider that statistical significance is attained by a quantity which equals twice its standard error—this may roughly be regarded as odds of 20 : 1 against the result being fortuitous.

The standard error of a percentage may be expressed as:

$$\sqrt{p(100-p)/n}$$

where p is the percentage and n is the total number. We may wish to discover the sex ratio at a given age in a particular district. Suppose that for this purpose we obtain a sample of 200 individuals, and find that 45 per cent of them are males. The standard error is calculated as 3.52, and the sex ratio should be expressed as 45 ± 3.52 . That is to say the chances are approximately 20 : 1 that the true sex ratio of the population from which the sample was withdrawn lies within the range 45 ± 7.04 . Moreover since the 50 per cent level falls within these limits, we have obtained no evidence that the sex-ratio of this population differs from equality. It may be noted that if we were actually concerned to test whether the observed frequencies were compatible with an expected ratio such as 50 per cent, we should calculate the error using that ratio

$$(i.e. \sqrt{50 \times 50 / 200} = 3.54)$$

This example shows not only that it is possible to estimate the relation of a sample to the population from which it was taken, but that an actual ratio may be compared with that expected to occur on some hypothesis. Therefore it is an

appropriate means of testing the significance of Mendelian ratios segregating into two classes. For with grouped data having a fixed total, the number of classes (V) to which an arbitrary value can be assigned $= V - 1$. This is called the number of *Degrees of Freedom*. Obviously a two-class Mendelian ratio is completely described by stating the total number of individuals, and that occurring in one class.

Suppose we collect 100 instances in which a character is segregating among the offspring of parents both of whom are of the dominant phenotype, and we find that 70 belong to the dominant class and 30 to the recessive. Does this differ significantly from a 3:1 ratio? The standard error is calculated as:

$$\sqrt{75 \times 25 / 100} = 4.43$$

The departure from expectation (of either class) is 5. This, being well under twice the standard error gives no ground for assuming that we are dealing with other than a normal 3:1 ratio.

This method is inapplicable to ratios of more than two classes, the significance of which must be tested by means of the χ^2 distribution (Fisher 1941). Furthermore, in human genetics particularly segregating ratios are often made up of a number of samples, some of which may be obtained in somewhat differing circumstances. It is highly important to determine if these all accord with one another or if they are heterogeneous, in which case they must not be pooled to provide a total. The χ distribution provides, in addition, a test of such heterogeneity and this should always be applied in such instances (see Mather 1938).

It was explained in Chapter I that the cross-over value (C.O.V.) is obtained by adding together the two cross-over classes and expressing them as a percentage of the total. Consequently the standard error of a percentage is an appropriate test of its significance, and should be employed for this purpose. We may take the example already studied (pp. 25-7), that of normal coat-colour dominant to albino, and white fat dominant to yellow fat, in the rabbit. The

to explain the procedure for doing so. The value of such work will, it is hoped, now be apparent.

An account of linkage and crossing-over was given in Chapter I, and it was pointed out on pp. 22-4, that accurate information on three generations is normally required in order to study these phenomena. This is rarely available in human material, so that it is important to realize that linkage data can now be obtained from an analysis of two generations or even a single one. Methods for studying linkage using two generations only have been developed by a number of workers, and now provide fairly accurate means for its detection in Man. A discussion of them is outside the scope of this book but an admirable account of the subject is given by Finney (1940-1). A less sensitive, but useful, test for linkage may be obtained from a single generation. It requires indeed a somewhat extensive study of brothers and sisters, but it is far more practicable to score two or three hundred individuals belonging to a single generation for the distribution of two contrasted characters than to do so on smaller numbers belonging to three distinct generations. The method of obtaining linkage data from the examination of a single generation is due to Penrose (1935). I regard it as an advance of great potential importance for human genetics. The procedure is not difficult, and may briefly be considered.

Two children from the same parents are classified for a given character for instance the presence of agglutinin A in the red blood corpuscles. Those alike in either respect (both with or both without A) are placed in one class, while unlike pairs (one with and one without A) are placed in another class. They are then similarly classified for any other unifactorial character. This is repeated for as many pairs of sibs (that is, children of the same parents irrespective of sex) as possible.

If the genes controlling the two sets of contrasted characters are unlinked, the four classes will appear in simple proportion. If, however they are linked, the two classes representing pairs which are alike or unlike in both respects will be in excess. The expectation on the assumption that

Linkage does not occur is obtained by the proportions of each class treated separately. An example will make the method clear.

Presence or absence of agglutininogen A

Presence or absence of red hair	Presence or absence of agglutininogen A		
	like	unlike	
	like	unlike	
like	40 (38)	17 (19)	57
unlike	0 (2)	8 (1)	8
	40	25	65

Table F. Classification of two characters for the detection of linkage. The values in brackets are those expected on the assumption of free assortment.

In Table F modified from Penrose (1935), 65 pairs of sibs are scored for the presence or absence of red hair and for the presence or absence of agglutininogen A in the blood. The numbers expected on the assumption of free assortment are entered in brackets below the actual numbers in each class. These expectations are obtained by dividing the total number (57) of sibs who are both alike in respect of hair colour (whether both red or both non-red) in the proportion in which the like and unlike blood-group classes are distributed (that is, 40 : 20). We thus obtain an expectation of 38 : 19. Similarly for the unlike pairs for hair-colour. These total 8 and, when distributed in a ratio of 40 : 20, give an expected distribution of 3 : 1. Naturally the proportions could equally well have been obtained by dividing the blood-group scores proportionately to the hair-colour classes. The data demonstrate a slight excess of even pairs (both alike or both unlike), as follows:

	even pairs	odd pairs	Total
observed	48	17	65
expected	39	21	60

The significance of the result can be established by calculating the standard error of the proportion, in the manner indicated in the last section. In this instance, the standard error = 8.7. It is, however, preferable to use the χ^2 distribution (Fisher 1941), for this test of significance. The departure from expectation is of the kind to be anticipated if linkage occurs, but it is not significant. Yet larger numbers might possibly demonstrate linkage between these genes.

This method is of the widest application. By its use, information on human linkage could readily be amassed.

Attention must be directed to an error which seems to be rather widespread in the interpretation of linkage. It is often noticed that two distinct characters are inherited together and I have repeatedly found this attributed to linkage between the two genes controlling them. It must be clearly understood that, in the population as a whole, linkage can never produce such a result. Crossing-over will usually separate linked genes from one another rather frequently. For the cross-over value is usually over 1 per cent; and even in exceptional instances of very rare crossing-over this process may be expected to occur at a level well above the mutation rate. In the general population, therefore, linked genes are just as often found dissociated as combined, and linkage provides no explanation at all for the inheritance of two characters together. Such a result can be produced by linkage only *within given families*. It is then due to the check imposed upon free assortment by the presence of two genes in the same chromosome; but this is a hindrance only not an absolute barrier. Indeed the tendency for two conditions to be associated within the same family though they appear independently of one another in the population as a whole, is a distinct indication of linkage. With this exception, the inheritance together of two distinct characters is attributable to the multiple effects of single genes, a phenomenon which has already been discussed (pp. 70-80).

III. THE DETECTION OF INHERITED CHARACTERS

The value of correlation in the study of heredity has already been discussed (pp. 67-8). It was pointed out that the correlation coefficient indicates the degree to which two variables are associated, such, for instance, as height and eye-colour. If, on the other hand, the association between the same character in different generations be studied the correlation coefficient becomes both a method for detecting inheritance and a comparative measure of its intensity. For the standard error of the difference between two correlation coefficients can of course be calculated, so that it can be determined whether the occurrence of a particular condition in one individual is accompanied by its occurrence in a relation more often than in a random sample of the population. The methods of calculating the correlation coefficient are given by Fisher (1941).

If a character is due to the operation of several genes, its segregation becomes undetectable even when their number is quite small (pp. 20-1). Here the method of correlation largely supersedes that of experimental breeding; but in an organism such as Man, in which experiments cannot be undertaken, correlation studies must be applied yet more widely. It is particularly to be noticed that they are applicable to all characters capable of measurement, of whatever kind. They therefore provide a test of the inheritance of mental and moral qualities, in so far as these can be assessed quantitatively. Various other types of numerical comparison are also available for this purpose.

The measurement of intelligence is, of course, a matter of much difficulty but the carefully devised Binet system seems to provide a just basis for estimating inborn ability in children, totally incapable as I believe it to be of application to normal adults. It is so adjusted that environmental and temperamental effects are largely excluded, so that the results obtained by its use are rather nearly proportional to the potential capacity of the children examined. They are expressed as a number called the *Intelligence Quotient* (I.Q.).

A valuable example of its use in genetics is provided by Fraser Roberts (1940 pp. 237-8). A group of 2,400 children of school age were given mental tests and classified as Bright (I.Q. >118), Average (I.Q. =91-118), and Dull (I.Q. <91). Three classes were then selected, comprising the brightest 4 per cent, the central 4 per cent, and the dullest 8 per cent. The sibs of school age of the children of these three groups were also tested. It was found that 63.8 per cent of the sibs of the brightest children were bright, and only 6.6 per cent were dull; while only 3.7 per cent of the sibs of the dullest children were bright, and 56.8 per cent of them were dull.

Such studies as these have clearly demonstrated that inheritance plays an important part in the development of mental characters. Analysis of a number of them suggest that perhaps 75 per cent of the variation in fundamental intelligence is genetic. It must of course be appreciated that *the use any individual subsequently makes of his mental endowments is largely environmental*, and quite outside the scope of such tests. It is undoubtedly true also that there is great variation in the rate of development of intellectual, as of physical qualities. Consequently children of apparently mediocre capacity may occasionally attain to high ability while many clever children do not fulfil their early promise. Environment must be an important factor in such changes, but the existence of genes controlling rates of development and the time of onset of processes in the body (pp. 96-7) indicates that heredity is also in part responsible for them.

The hereditary component in the control of intelligence is particularly important inasmuch as mating is far from being at random in respect of mental qualities. There is a strong tendency for the more and the less intelligent members of the community respectively to marry those who approximate to their own mental level.

In general, there can be no doubt that ordinary mental qualities are controlled by normal genetic means, being determined jointly by heredity and environment, as are physical characters. So too are such conditions as tendencies

to crime and vagrancy a fact well demonstrated by the work of *Lidbetter* (1933).

The study of twins plays an important part in the detection of inherited conditions in Man. Two types of twins exist, fraternal and identical, and the tendency to produce one or the other of them is inherited. Fraternal twins are due to the simultaneous ovulation of two eggs, both of which are fertilized. They may therefore be either similar or dissimilar in sex, and they are no more closely related to one another than are ordinary brothers and sisters. Identical twins, on the other hand, arise from a single fertilized egg, which splits into two at an early stage in development. Therefore they must be of the same sex and contain identical genes. The distinction between these two types is usually self-evident. Fraternal twins differ in many respects, while identical twins are almost indistinguishable. Here and there doubtful instances are found, but a thorough examination will usually decide to which class they belong: this should include as many physical features, known or presumed to be genetically controlled, as possible, also such physiological characters as the blood-groups and the taste test.

Fraternal twins, though no more alike genetically than ordinary brothers and sisters, tend to live in a more similar environment than they. Statistical studies on the differences between such twins and between normal sibs are therefore of service in determining the effect of environmental variation. Far more important, however are comparisons between the two classes of twins. The differences between the members of identical pairs are purely environmental, genetic variation being wholly absent. They are of course subject to a more similar environment than are normal sibs, but not more so than fraternal twins, so that they allow a rather precise measure of the importance of environment in producing variation, whether physical or mental, and the similarity of the identical type indicates how large a part is attributable to heredity.

Twin studies are of service in other ways, and these are

well illustrated by a useful comparison between the genetics of tuberculosis and pneumonia, drawn by Fraser Roberts (1940). If a number of twins be studied, one of whom suffers from tuberculosis, the frequency with which the other member is also a tuberculosis patient is much higher in the identical than in the fraternal type. Heredity is therefore important in determining susceptibility to the bacillus, but the environment is also a factor since one member of a pair of identical twins may sometimes be tuberculous when the other is not. Further in the latter circumstances the prognosis of the disease is particularly hopeful since, as Fraser Roberts points out, the affected individual has succumbed in spite of a high resistance. It is noteworthy also that the site of the lesion is partly determined by hereditary agencies, since this is more often the same in pairs of identical than of fraternal twins. These facts are to be contrasted with the frequency with which pneumonia affects pairs of twins: this is scarcely any higher in the identical than in the fraternal type. Clearly heredity is not an important agent in predisposing to that disease.

When a syphilitic woman gives birth to fraternal twins, it is sometimes found that one member only of them suffers from congenital syphilis. This is strong evidence that susceptibility to it is in part due to the action of genes.

The occurrence of consanguineous marriages provides valuable material for detecting rare recessive conditions in Man. It is a proposition of general application that, with particulate inheritance, inbreeding tends to produce homozygosity. Where self fertilization occurs, as in plants, the proportion of heterozygotes is actually halved at each generation; for those individuals already homozygous remain so while half the offspring of the heterozygotes are homozygotes. Less close degrees of inbreeding produce homozygosity much less rapidly but none the less definitely. If an individual is a heterozygote for some rare recessive autosomal condition, the chances that his brother or sister is a heterozygote are 1 : 1, that a first cousin is one also.

When a recessive condition affects one individual in 10,000, 2 per cent of the population are heterozygotes (p. 120), and if one of these marries an unrelated person the chances against his wife being heterozygous also are 1:49 but they are 1:7 if he marries a first cousin. In these circumstances, the chances that the condition shall appear among the offspring are increased sevenfold by a first cousin marriage. If we consider the population as a whole, one individual in fifty is a heterozygote, so that one marriage in 2,500 is capable of producing the homozygous recessive (which appears in one quarter of the offspring), but one first-cousin marriage in 400 can so do: the frequency is 6.25 times increased thereby.

These facts indicate that rare recessives must appear among the offspring of consanguineous marriages far more often than in the general population. The frequent occurrence of consanguinity between the parents of those suffering from a rare disease is a diagnostic sign of much importance. It strongly suggests that the condition is inherited as a simple recessive. In England about 0.6 per cent of all marriages take place between first cousins. Yet over 30 per cent of those suffering from alkaptonuria (p. 97) are the offspring of first-cousin marriages!

Finally it is necessary to mention a fruitful source of error in the collection of genetic data. If a character is an autosomal dominant half the children who have one affected parent will on the average possess it. But some families will contain too many affected individuals and others will contain none. These in reality cancel each other out but, in recording such family groups, those without affected individuals will be omitted. This will make the condition appear to segregate in excess of the expected equality.

Such an effect is unimportant for genes having heterozygous expression, since the appearance in certain families of a character in approximately half the individuals of successive generations will make its method of inheritance obvious. But for recessive characters the corresponding error is serious.

unless very common, the vast majority of recessives have normal parents, while their expected family incidence is only 1:8. Therefore many families in which both parents are heterozygous will have no affected children, and will be omitted in collecting data. The average frequency per affected family will consequently be much too high, and this is accentuated by the fact that families with many affected members are more likely to be recorded than those with few. Thus it may unjustifiably be doubted if the situation is one of simple unifactorial inheritance. Statistical methods, however exist which help to reduce these sources of error.

IV EUGENICS

It was shown in the first section of this chapter that the genes responsible for very rare recessive conditions are extremely widespread in the population. Furthermore, it will be recalled that most mutations are disadvantageous in effect, and that unfavourable characters tend to become recessive (Chapter IV). Very large numbers of such genes must therefore exist in Man. Consequently we can be sure that each individual will be heterozygous for some of them. It is for this reason that only close inbreeding is generally harmful, so that prohibitions against it exist in the laws of most countries. There is nothing mysterious about the effects of brother and sister marriages, and in an ideally sound stock, one which carries few disadvantageous genes, they would not have undesirable consequences. Their danger is simply due to the generalization already made that inbreeding tends to produce homozygosity with its consequent segregation of disadvantageous recessives.

These facts indicate how difficult must be any extensive programme of eugenic reform. It is absolutely impossible to rid a population of a disease inherited as a simple recessive. Obviously this cannot be done by preventing all who suffer from it from having children, because the heterozygotes are indistinguishable. But even if they could be detected, the gene would be so widely spread that its extermination would be out of the question. Nor is the situation at all simple in

respect of the heterozygous conditions (the so-called dominants'). These could be eliminated by this means in a single generation, but only in one group of instances is it worth attempting to do this, or rather to lower their incidence by preventing the procreation of at least a proportion of affected persons.

From the point of view of eugenics, heterozygous defects must be grouped into two classes: those which reduce significantly the number of children born to affected individuals, and those which do not. The first of these, of which Darier's Disease is an example, could never be diminished materially in the population by eugenic methods, because the genes controlling them must be distributed with a frequency not greatly above their mutation-rate. Consequently any one of them would soon be established again at its former level even after its complete elimination. The second group of heterozygous defects, those which have but a slight influence in the number of children born, present a legitimate field for the application of eugenic measures. It includes even a few severe diseases, being those whose first symptoms appear after the average age of reproduction, of these Huntington's Chorea is an instance.

However L. Darwin (1928) had stressed that the most valuable opportunities for eugenics are provided by multifactorial conditions, which actually allow of more rapid selective improvement. Mental deficiency is usually of this type, though it may also be unifactorial. It is of great importance, affecting as it does about 1 per cent of the population, while it tends to increase, rather than to decrease, the number of children born. It is certainly true that a programme of sterilization could materially reduce its incidence.

Of all inherited evils, insanity presents not only one of the most pressing but one of the most difficult problems. For it is easy to damage the working of a delicately balanced system like the human brain in a variety of ways. Thus it comes about that many different genes may all produce apparently similar forms of mental defect. Only here and

there, when one of them chances to give rise to some recognizable additional character can the unifactorial nature of a type of mental deficiency be detected, as in epilepsy or phenylketonuria.

It must not be supposed, however that no advice of a eugenic nature can safely be given. Indeed such advice has already been offered on a number of occasions in this book. Those who belong to a family in which a sex-linked disorder occurs will now know what type of risks they run in marriage. Those who suffer from a defect inherited as a simple dominant must realize that they will transmit the gene responsible for it to half their children. In certain instances they may well question whether they ought to produce offspring. It is particularly important that those who belong to a family in which a dangerous recessive disease has appeared should not marry a near relation. To abstain from so doing is an evident duty. The reason for this will now be clear and it will be clear also how greatly linkage studies will help those who are faced with such personal problems as these.

We have so far been occupied with negative eugenics' the elimination of disadvantageous characters. There exists also the question of 'positive eugenics' the dissemination of advantageous ones. Among animals such a process is quite practicable, and it has been successfully applied. Close inbreeding, brother and sister mating for example, not only causes the segregation of disadvantageous recessives but, if combined with the elimination of the unfit, purges the race of them. By constant repetition of the process in two lines, rather invariable stocks can be built up each containing relatively few harmful genes. A single 'out-cross' between them ensures much segregation and a wide range of variation, from which the best strains can be selected and maintained safely by inbreeding.

Such a procedure is obviously inapplicable to Man. Moreover we have at present such poor criteria for deciding what human types are advantageous. Some of us have encountered the conjunction of a weakly body and great brain, and we are all familiar with its depressing converse.

Left to human judgment, it is certain that the genius would often never have been born. On a minor scale, a clever man should seek in marriage a partner whose mental powers are good, for we have seen that, on the average, they will produce intelligent children; but an extensive programme of positive eugenics is one for the distant future.

The question of eugenics reform encroaches upon one of the special preserves of the fanatic, the problem of Race. To some in these days, it has become a creed that such concepts as the British, the Nordic, or the Jewish races have, or have not, reality. In this matter as in many others, extreme views appear to be incorrect.

On the one hand, it is not admissible to maintain that such races are purely artificial. Their characters have some reality and we have good evidence that they may be preserved when one people is immersed among others. It has already been mentioned that the blood-group frequencies of Dutch and Russian Jews are much more alike than are those of the communities among whom they live (p. 107). On the other hand particulate inheritance allows the maintenance within each race of vast reserves of variability capable of producing, without racial mixture, far greater diversity than that separating any of them. Recurrent mutation allows the genes of one race to appear in another; and so great a part of their gene-complex have even the most diverse of the human races in common, that no shadow of specific distinction can be detected even between the most dissimilar of them (p. 81). The proportion of genetic material which is different in the more nearly allied races cannot be great.

An accurate basis for the race-concept, in so far as this is attainable, should reflect the time available for the accumulation of genetic diversity. It might be reasonable to suggest, for example, that Englishmen had half their ancestors in common fifty generations ago, and that we should have to go back seventy-five generations before this was true of both Englishmen and Frenchmen. It is probable that the most remote of the races are, judged from this point of view many times older.

The methods suggested in this chapter provide the means for increasing rapidly our knowledge of human heredity. Additional data rather than new techniques are at present the chief need. I hope that some medical practitioners will feel that it is worth while to devote time and trouble to obtaining such information. It is my belief that it can be used for the benefit of mankind.

APPENDIX I

CYTOLOGY

CYTOLOGY is the study of cell structure, and I have so far assumed that the reader possesses such a knowledge of it as is normally acquired by medical students at an early stage in their career. It may be, however that some who have no acquaintance with the subject may wish to read this book. Furthermore, great advances have been made in nuclear cytology during the last twenty years. Those who suspect that their information on mitosis, and especially meiosis, is somewhat out of date, may possibly desire to revise it. I have therefore prepared this brief summary of the relevant aspects of cytology. All who require a more detailed account should consult the fundamental work of Darlington (1937). I also wish to recommend the excellent little treatise by White (1937).

() THE RESTING STAGE

The living substance of the body is called protoplasm, and this is normally divided into microscopic units called cells. Each cell is composed of two parts, a nucleus which controls its activity and the remaining protoplasm, called cytoplasm. The protoplasm of the nucleus, known as nucleoplasm, is enclosed in a 'nuclear membrane'.

Tissues grow by a multiplication of their cells, not by an increase in cell size. The nucleus contains the chromosomes, and these carry the hereditary units or genes (Chapter I). Therefore it is a matter of the utmost importance that the chromosomes should be so distributed at cell division that each of the two new cells into which the old one splits should possess a complete set of them. Normal nuclear division is called mitosis. A cell which is not dividing is said to be in the 'resting stage': since it may then be in a state of physiological activity this term is unfortunate.

The chromosomes are usually though not quite always, invisible in the resting nucleus when alive. Cells are usually studied by 'fixing' them (that is to say killing them with as little distortion as possible) and staining them with dyes which colour their parts differentially. Owing apparently to its high water

in muscle and in the brain, however, increase in bulk does result from an increase in cell size.

The methods suggested in this chapter provide the means for increasing rapidly our knowledge of human heredity. Additional data rather than new techniques are at present the chief need. I hope that some medical practitioners will feel that it is worth while to devote time and trouble to obtaining such information. It is my belief that it can be used for the benefit of mankind.

granule, called the centrosomes, lies outside the nuclear membrane. At the end of the prophase, its two parts separate and move to opposite sides of the nucleus. They remain in connexion, however by a modified region of cytoplasm called the 'spindle'. At the beginning of the prometaphase, the nuclear membrane disappears and the spindle sinks inward until its axis occupies a line between the two centrosomes. Each chromosome then organizes the nuclear sap into additional spindle elements which coalesce round the original spindle, increasing its bulk. As finally formed therefore, the spindle is composed of two distinct parts.

Structures called 'spindle fibres' running from the chromosome to each pole, were formerly described. Indeed it was even stated that by their contraction the two chromatids were eventually pulled apart. It is now known that no such fibres exist. When apparent, they are probably due to the shrinkage of the spindle during fixation, causing cracks to appear between its separately organized nuclear components.

Metaphase. At this stage, the chromosomes lie on the equator of a system whose poles are the centrosomes, and they are 'attached' to the spindle there. That is to say they are associated with the peripheral spindle elements of nuclear origin which they have themselves organized. It seems that they never come into relation with the central spindle formed of extra nuclear material which, in fact, does not exist in all forms. The attachment of the chromosomes to the spindle is secured only at their spindle attachments, and their long arms stretch out into the cytoplasm. If a chromosome breaks into two parts, only that containing the spindle attachment becomes anchored to the spindle, the other portion floats away and is lost when the cell divides.

The two chromatids forming each chromosome lie even closer together in the metaphase than in the prophase. Consequently the split separating them is no longer apparent except in transverse section, when the chromosomes assume the shape of figures of eight. Special methods show that the chromatids have the form of tightly coiled springs within thin pellicles. At this time, its turns are normally in contact, but they can be separated slightly from one another so revealing the chromatid structure. The pairs of chromatids are coiled independently of one another. This spiral structure develops during late prophase and the prometaphase. It persists for the remainder of mitosis and, when the resting stage is short, some relic of it may still be visible at the beginning of the next prophase.

Anaphase. The metaphase is a period during which very little change occurs. Usually it is of short duration. The onset of anaphase is marked by the splitting of each spindle attachment into two parts. These then repel one another so that the two chromatids forming each chromosome are dragged apart in opposite directions towards the poles of the spindle. Thus the prophase chromatids become the anaphase 'daughter chromosomes'. When the two sets have moved some distance from one another their separation is completed by a change in the equatorial region of the spindle. This elongates, forming a so-called 'stem body' which pushes the two sets of daughter chromosomes yet farther apart.

Telophase. When the two groups of daughter chromosomes have separated widely they come to rest and undergo a series of changes the reverse of those which took place in the prophase. A nuclear membrane forms, the chromosomes take in water swell, and become increasingly difficult to fix and stain. Finally they can no longer be demonstrated by this means. The nucleus has then returned to the resting stage.

Either during late anaphase or telophase, the cytoplasm constricts between the two newly formed nuclei, which are thus enclosed within separate cells. Each of them therefore possesses a complete set of undivided chromosomes. These contain the full complement of genes, since they were produced by the longitudinal splitting of chromosomes which had grown to double their original thickness. It will be remembered that this occurred during the previous resting stage. Mitosis is now complete, and the new daughter chromosomes will themselves grow until they also split into chromatids shortly before the next cell-division.

(III) MEIOSIS

During the formation of the gametes, an interchange of material takes place between the paternally and maternally derived members of the pairs of homologous chromosomes, resulting in genetic crossing-over while the chromosome number is reduced from the diploid ($2n$) to the haploid (n). This is brought about by a special process called meiosis. It consists of two highly modified cell-divisions, being the last which the germ-cells undergo.

Meiosis is defined by Darlington as 'two divisions of the nucleus with but one division of the chromosomes'. Thus it comprises a first meiotic division and a second meiotic division. These will

now briefly be described. Those features, such as spindle formation, which they possess in common with mitosis will be omitted.

(a) *The first meiotic division*

Prophase

The prophase of the first meiotic division is abnormal and complex. It is subdivided into four parts, the leptotene, zygotene, pachytene, and diplotene stages.

Leptotene stage. The chromosomes appear as very long, thin threads which are not yet split into chromatids, as they would be at the beginning of a mitotic prophase. A series of darkly staining granules, whose position is constant for a given chromosome, can be detected along their length. These are called *chromomeres*. It is supposed that they may represent the genes.

Zygotene stage. The homologous chromosomes come together in pairs. This is due to an attraction between identical chromomeres. It does not result from an attraction between whole chromosomes, for these remain unpaired in the region of an inversion (p. 60). As a consequence of this pairing, the haploid number () of double bodies, called *bivalents*, is formed. These have a split along their length, and they therefore much resemble the chromosomes of a mitotic prophase. The fact that they possess two spindle attachments, however indicates their very different nature.

Pachytene stage. This comprises the period during which the homologous chromosomes are associated as bivalents. It may last for a considerable time. At first, the members of each bivalent lie parallel, but they soon twist round one another. During pachytene, the chromosomes split into chromatids. As already explained, they normally do so before cell-division starts, but the first meiosis is precocious, for the resting stage preceding it is short or incomplete. Consequently the chromosomes are not ready to divide until the prophase is well advanced.

Diplotene stage. It seems that the force which brings about and maintains chromosome pairing in meiosis is the same as that which keeps together the two chromatids forming each chromosome during the mitotic prophase. This is an attraction of homologous units in pairs. But whole chromosomes no longer attract one another after they have split in pachytene, for the attraction is transferred to the pairs of chromatids composing them. Indeed the chromosomes themselves then tend to drift

apart, owing to a surface repulsion. However they are prevented from doing so completely because they are held together at certain points where they have interchanged material. These are called *chiasmata*, and their formation must briefly be described.

The four chromatids forming the two chromosomes of a homologous pair are called a *tetrad*. Two of them, derived respectively from the different members of the pair, may interchange material at a point, while the other two remain intact. This interchange of material produces genetic crossing-over. Since it is not accompanied by an interchange of partners, two of the four chromatids must cross over one another in the form of an X, whence the name 'chiasma' (Fig 10). At least one chiasma nearly always forms between any pair of chromosomes, and the average number



Fig 10. Chiasma formation.—A single chiasma has formed between a pair of homologous chromosomes. These are each composed of two chromatids which are still united at the spindle attachment, here represented near one end. It will be seen that the chiasma involves two chromatids, derived from different homologous chromosomes, which interchange material but not partners at point, while the other two remain intact.

may even be as high as eight. However they do not occur very near together because the chromatids are stiff enough to resist close twisting. The occurrence of one chiasma therefore prevents the formation of another in its immediate neighbourhood involving the same chromatid. Consequently double crossing-over does not take place between genes which lie near to one another whence the phenomenon of 'interference' (p. 28). Complete cytological proof has now been obtained that the chromatids do not merely twist over one another where a chiasma forms, but that they actually interchange material at that point (see Darlington, 1937). Unless this were so, chiasma formation could not provide the physical basis of genetic crossing-over.

After the chiasmata have formed, the chromatids shorten and thicken as in mitosis, and they rotate through about 180 degrees. Generally also the visible chiasmata (the points at which the chromatids pass over one another to form an X) tend to slide away from the spindle attachment towards the ends of the

chromosomes. This is called *terminalization*. Obviously it does not affect the situation of the interchanged segments, but merely the position of the twist resulting from that interchange.

The prophase is followed by a fairly normal prometaphase.

Metaphase

This resembles the metaphase of a mitosis. It will be realized, however that each bivalent ("tetrad") possesses two spindle attachments, one paternally and one maternally derived.

Anaphase

The spindle attachments do not now divide, as they do in mitosis. When, therefore, those of homologous chromosomes begin to repel one another they drag apart pairs of chromatids. Consequent upon chiasma formation, these contain sections both of paternal and of maternal origin.

Both in mitosis and in the first meiosis, the diploid number of bodies move from the equator towards each pole in anaphase. In mitosis, these are the diploid number of undivided chromosomes, but in the first meiosis they are the haploid number of chromosomes divided into pairs of chromatids (which are yet held together at the spindle attachment). The separation of the chromosome sets and their movement towards the poles of the spindle is brought about as in mitosis.

Telophase

This does not differ materially from a normal mitotic telophase. It may or may not be followed by brief resting stage, called an *interphase*.

(b) The second meiosis

If there has been no interphase, a second meiotic prophase is not needed, and the telophase of the first meiotic division passes directly into the prometaphase of the second. The occurrence of an interphase necessitates second meiotic prophase, but this is short and exhibits no very noteworthy features.

Prometaphase

This differs from that of a mitosis in two respects only. The chromosomes are of the haploid number while the chromatids into which each is split are only held together by their spindle attachments; elsewhere they diverge widely.

The metaphase, anaphase, and telophase call for no special comment. It will readily be appreciated that they result in the production of gametes containing the haploid number of undivided chromosomes.

(c) *General survey of meiosis*

In general, it may be said that meiosis consists of two highly abnormal cell-divisions, modified from the mitotic plan. Their evolution has largely been dependent upon an alteration in timing, such that the chromosomes do not split into chromatids until the first prophase is well advanced. This is responsible for chromosome pairing (p. 145).

Meiosis allows an interchange of material to take place between homologous chromosomes, and is therefore responsible for genetic crossing over. It also reduces the chromosome number from the diploid to the haploid. Formerly it was held that meiosis comprises a single 'reduction' division (the first meiosis) and that this is followed by a mitosis (which corresponds to the second meiosis). Such a view is totally incorrect. The reason for this reveals very clearly the fundamental distinction between mitosis and meiosis, and is therefore worth brief consideration.

The essential function of nuclear division is genetic. A mitosis is an 'equating' division—one which ensures that the 'daughter' cells shall each receive the same number of genes as that possessed by the cell from which they were derived. Meiosis is 'reducing' because it brings about Mendelian segregation. If no chiasmata were to form, the whole of segregation would be effected at the first meiosis, so that the succeeding division (the second meiosis) would be purely equating and therefore mitotic in type. Owing to chiasma formation, however, segregation takes place at the first or the second meiosis alternately as we pass from one interchanged segment to the next, starting from the spindle attachment. The last cell-division before the gametes are formed is therefore just as much concerned in effecting Mendelian segregation as is the penultimate one. Thus it is a second meiosis, not a mitosis.

APPENDIX II

CLASSIFIED LIST OF SOME INHERITED
CHARACTERS IN MAN

THIS LIST is limited to conditions ascertained on fairly good evidence to be determined at least principally by a single main gene. It is not intended to be complete, and in fact it excludes large number of characters known or presumed to be unifactorial (information on these may be obtained from the works cited in the Bibliography). In addition, multifactorial inheritance has been studied extensively in Man, but the results cannot so usefully be summarized in tabular form.

The characters are arranged in groups, distinguished by letters. Within each of these they are placed in alphabetical order and numbered. This allows cross-references to be given when similar characters are produced by different genes.

Caution must be exercised in using this list. In some instances, environmental agencies may modify the expression of a gene. Further conditions whose genetics are clearly established may sometimes be inherited in an exceptional way. This may be due to the ordinary gene operating in an unusual gene-complex, or to the action of a distinct gene having superficially similar effects. For example, though albinism is well known to be recessive, dominant albinism has been reported as a great rarity. As already explained (p. 17), no evidence exists that the majority of the so-called 'dominant' characters in man are produced by genes having identical effects in the heterozygous and homozygous states.

Abbreviations are used to give further information on those characters which are particularly subject to various irregularities, as follows:

- Probably some complications.
- β — Occasional heterozygous manifestation.
- γ — Occasionally not expressed in heterozygote.
- δ — Dominance incomplete.
- Expression markedly variable.

A. SIMPLE RECESSIVES

- | | |
|------------------------------------|---|
| 1. albinism. | 11. Laurence-Moon-Biedl syndrome (). |
| 2. alkaptonuria. | 12. Epithelioma of skin. |
| 3. amaurotic idiocy infantile. | 13. phenylketonuria. |
| 4. amaurotic idiocy juvenile. | 14. phenyl-thio-urea, inability to taste. |
| 5. atheroma (B5). | 15. polydactyly (B33). |
| 6. blue or gray eyes (a). | 16. porphyria congenita. |
| 6a. deaf-mutism. | 17. red hair (a). |
| 7 ear-lobes adherent. | 18. retinitis pigmentosa, with deafness. |
| 8. Friedreich's ataxia. | 19. a, no secretion of antigens A and B. |
| 9. hare-lip and cleft palate (F3). | |
| 10. ichthyosis congenita. | |

B SIMPLE DOMINANTS

- | | |
|--|--|
| 1. A, B blood-group series. | 31. haemophilia-A. |
| 1a. acholic jaundice. | 32. Huntington's chorea. |
| 2. achondroplastic dwarfing | 33. ichthyosis vulgaris (γ) (D4). |
| 2a. allergy (δ excess). | 34. infection, absence of. |
| 3. androtic ectodermal dysplasia (D1). | 34a. jaundice, acholic. |
| 4. aplasia cutis congenita. | 35. keratoderma. |
| 5. atheroma (γ), (A5). | 36. nasal sinus infection, an extreme tendency |
| 6. auditory nerve atrophy | 37. neurofibromatosis. |
| 7 bone fragility and blue sclerotics. | 38. night blindness. |
| 8. brachydactyly | 39. oedema, angioneurotic (non-allergic). |
| 9 cantiles praematura. | 40. Osler's disease. |
| 10. cataract, congenital. | 41. phalangeal synostosis. |
| 11. cholesterosis cutis. | 42. piebalding. |
| 12. coloboma iridis. | 43. polydactyly (c), (A15). |
| 13. Darier's disease. | 44. porokeratosis (excess of δ incidence). |
| 14. defective enamel of teeth. | 44a. premature baldness (limited to δ). |
| 15. diabetes insipidus (γ). | 44b. rectal polyp. |
| 16. epidermolysis, simple. | 45. retinitis pigmentosa, without deafness (D2, F4). |
| 17. epidermolysis, mild dystrophic (a, γ). | 45a. Rh antigens. |
| 18. epikola (c). | |
| 19. epithelioma, benign cystic. | |
| 20. glaucoma (a, γ). | |

- | | |
|--|--|
| 36. sebaceous cysts, multiple. | 41. white forelock (B42). |
| 37. splastic paraplegia (F5). | 42. white forelock (restricted to males), (B41). |
| 38. split foot. | 43. woolly hair (in Europeans). |
| 39. teeth, supernumerary | |
| 40. tylosis palmaris et plantaris (7). | |

II INTERMEDIATE HETEROZYGOSES

- | | |
|--|------------------------|
| 1. curly straight, wavy hair (in Europeans) (a). | 2. minor brachydactyly |
| | 3. M, N blood-group. |

D SEX LINKED RECESSIVES

- | | |
|--|--|
| 1. anhidrotic ectodermal dysplasia (B3). | 5. 'incomplete albinism. |
| 2. colour blindness, red green (5). | 6. macula lutea, absence of |
| 3. haemophilia (9 allelomorphs). | 7. microphthalmia (1 family). |
| 4. ichthyosis vulgaris (B33). | 8. optic nerve atrophy hereditary |
| | 9. retinitis pigmentosa, without deafness (B35, F4). |

E SEX LINKED DOMINANTS

- | | |
|-------------------------------------|--|
| 1. missing incisors (1 family) (c). | 2. nystagmus (only about 80 per cent heterozygous expression) (c). |
|-------------------------------------|--|

F PATAL SEX LINKAGE

- | | |
|--|---|
| 1. epidermolysis, severe dystrophic (recessive). | 5. spastic paraplegia, recessive (B37). |
| 2. hare-lip and cleft palate (recessive) (A9). | 6. total colour blindness (recessive). |
| 3. Oguchi's disease (recessive). | 7. xeroderma pigmentosum (recessive). |
| 4. retinitis pigmentosa, without deafness [9 allelomorphs, 1 dominant, 1 recessive] (B35, D9). | |

G TOTAL X LINKAGE IN Y

- | | |
|------------------------------|--------------------------|
| 1. ichthyosis hystrix graeca | 2. webbed toes (1 form). |
|------------------------------|--------------------------|

APPENDIX III

THE Rh GROUP (continued from p. 114)

IMPORTANT INFORMATION on the Rh group has been obtained since this book was first published. As it is not yet available save in original papers, and as essential treatment may now be based upon the genetic findings, I have decided to give a brief summary of certain aspects of this work in an Appendix (for fuller details, see Taylor, 1944).¹

Hæmolytic disease of the new-born most commonly manifests itself as icterus gravis neonatorum. It also produces some of the still-births occurring after the twenty-eighth week, though it is seldom involved in pregnancies ending earlier. The Rh agglutinin is only produced in Rh negative individuals. In them it may appear as a result of transfusion by Rh positive blood, or of a pregnancy in which the foetal blood is Rh positive, that condition being inherited from the father. In one marriage in eight the husband is Rh positive and the wife Rh negative.

First-born children usually escape hæmolytic disease, and there may be several normal births before an affected child appears, for the Rh antibody can remain for years in the maternal blood and thus accumulate from several pregnancies. If the husband is heterozygous for the gene, alternate births will, on the average, be normal. Hæmolytic symptoms rarely occur unless the husband is homozygous, as three out of seven Rh positive men will be, since sufficient Rh antibody is seldom formed when half the pregnancies are Rh negative. Consequently parents should understand that when once an affected child has appeared, the chance of bearing healthy children again is remote. Appropriate treatment, however, gives good results.

Preliminary steps should be taken during the subsequent pregnancies and, as a precaution, this should also be done whenever a husband is Rh positive and his wife Rh negative, especially if there have been still-births. This should consist in ensuring that a supply of O, Rh negative blood is available at birth. If there is any sign of hæmolytic disease, the child should at once be transfused with such blood into a vein, until an erythrocyte level of 5,000,000 is reached. To provide this, together with a reserve, about 250 c.c. will be required, and a further transfusion may be needed. This should supply erythrocytes until the antibody in the child's serum is used up, and the result is highly satisfactory.

¹Taylor, G. L. (1944) *British Encyclopædia of Medical Practice*, Interim Supplement 23.

BIBLIOGRAPHY

THE FOLLOWING short list of works has been selected to provide further information on the subjects discussed in the various chapters of this book. When no Section Number is appended, it is to be understood that the reference is applicable to the chapter as a whole.

CHAPTER I.

Stenott, E. W., and Dunn, L. C. (1932, 3rd Edn.) *Principles of Genetics*, New York.

Waddington, C. H. (1930) *An Introduction to Modern Genetics*, London.

CHAPTER II.

SECTION I.

[Various authors] (Editor E. Allen) (1932, 2nd Edn.) *Sex and Internal Secretions*, London.

SECTION II.

Roberts, J. A. Fraser (1940) *An Introduction to Medical Genetics*, Oxford.

SECTION III.

Crew F. A. E. (1937) 'The Sex Ratio' *Rep. Brit. Ass.* (Nottingham), pp. 95-114, London.

CHAPTER III.

Fisher R. A. (1930) *The Genetical Theory of Natural Selection*, Oxford.

Ford, R. H. (1936) *The Study of Heredity* (see Chapter V), Home University Library

Goodrich, E. S. (1934) *Living Organisms*, Oxford.

Timofeeff Resovsky N. W. (1934) 'The experimental Production of Mutation' *Biol. Rev.*, 9, 411-57

CHAPTER IV

SECTIONS I and III.

Ford, R. H. (1940, 2nd Edn.) *Mendelism and Evolution* (see Chapter II), London.

Goldschmidt, I. L. (1938) *Physiological Genetics*, New York.

SECTION II.

Fisher R. A.: (1930) *The Genetical Theory of Natural Selection*, Oxford.

SECTION IV

Roberts, J. A. Fraser: (1940) *An Introduction to Medical Genetics*, Oxford.

CHAPTER V

Ford, H. M.: (1940) 'Polymorphism and Taxonomy' in *The New Systematics*, Oxford.

Wiener A. S.: (1939, 2nd Edn.) *Blood Groups and Blood Transfusion*, London.

CHAPTER VI.

SECTION I.

Fisher R. A.: (1941, 8th Edn.) *Statistical Methods for Research Workers*, Edinburgh.

Mather K.: (1938) *The Measurement of Linkage in Heredity*, London.

SECTION III.

Roberts, J. A. Fraser: (1940) *An Introduction to Medical Genetics*, Oxford.

SECTION IV

Fisher, R. A.: (1930) *The Genetical Theory of Natural Selection* (see Chapters VIII to XII), Oxford.

APPENDIX I.

Darlington, C. D.: (1937 2nd Edn.) *Recent Advances in Cytology* London.

White, M. J. D.: (1937) *The Chromosomes*, London.

APPENDIX II.

Baur E., Flecher E., and Lenz, W.: (1931) *Human Heredity*, London.

Cockayne, E. A.: (1933) *Inherited Abnormalities of the Skin and its Appendages*, Oxford.

Roberts, J. A. Fraser: (1940) *An Introduction to Medical Genetics*, Oxford.

REFERENCES

- BAUR, K., FISCHER, K., and LEWIS, Y. (1931) *Human Heredity* London.
- BELL, J., and HALDANE, H. E. (1937) 'The Linkage between the Genes for Colour blindness and Haemophilia in Man' *Proc. Roy. Soc. B.*, 182, 119-30.
- BENEDICT, F. G., and KEMMER, L. E. (1915) 'A Comparison of the Basal Metabolism of Normal Men and Women' *J. Biol. Chem.*, 20, 253-62.
- BENEDICT, F. G., and TALBOT, F. E. (1921) 'Metabolism and Growth from Birth to Puberty' *Carnegie Inst. Wash. Publ.*, 302, pp. 213.
- BOLK, L. (1926) *Das Problem der Menschwerdung*, Jena.
- BOYD, W. C., and BOYD, L. G. (1937) 'Sexual and Racial Variations in ability to taste Phenyl-Thio-Carbamide—' *Ann. Eng.*, 8, 48-51.
- BURKE, H. E. (1933) 'Autosomal Linkage in Man' *Proc. Nat. Acad. Sci.*, 24, 513-19.
- COCKAYNE, E. A. (1933) *Inherited Abnormalities of the Skin and its Appendages*, Oxford.
- CREW, F. A. E. (1937) 'The Sex Ratio' *Rep. Brit. Ass. (Nottingham)*, pp. 25-114, London.
- CHIK, L., and MATHER, K. (1938) 'The Sex Incidence of certain Hereditary Traits in Man' *Ann. Eng.* 9, 128-45.
- DARLINGTON, C. D. (1937 2nd Edn.) *Recent Advances in Cytology*, London.
- DARWIN, L. (1935) *The Need for Eugenic Reform*, London.
- FORNEY, D. J. (1940-1) 'The Detection of Linkage' *Ann. Eng.* 10, 171-214; 11, 10-30 and 115-25.
- FREMER, E. A. (1939) 'The Possible Modification of the Response of the Wild Type to Recurrent Mutation' *Am. Nat.*, 62, 115-30.
- (1930a) *The Genetical Theory of Natural Selection*, Oxford.
- (1930b) 'The Distribution of Gene Ratios for rare Mutations,' *Proc. Roy. Soc. Edinb.*, 50, 204-19.
- (1931) 'The Evolution of Dominance' *Biol. Rev.*, 6, 245-62.
- (1935) 'Dominance in Poultry' *Philos. Trans. Roy. Soc. B.*, 225, 197-222.

- Deletion, 80
 Diabetes insipidus, 87 98, 180
 mellitus, 87
 Dihybrid, 72
 Diploid, 142
 Diploids, 142
 Domestication, 87-8
 Dominance modification, 88-90,
 121
 human, 87-8
 Dominant, 10, 12, 17, 84, 137-8
 Drosophila, 24, 51 82, 84, 72, 80
D. melanogaster 72, 128-7
D. pseudo-obscura, 88
 Dunn, 9, 60
 Dysphasia, 80

 Earlobes, 160
 Eczema, 86
 Emura, 86
 Endocrine organs, 86
 Environment, external, 90-8
 inherited effects, 71-8
 internal, 80-2
 optimum, 81
Epidermophyton *trichosporum*, 80-1, 78-8,
 150-1
 Epilepsy, 78-80, 84-8, 128, 160
 mutational rate, 83
Epithelium, *dermis*, 180
 Equating divisions, 142, 148
Erythroblastosis foetalis, 114
 Erythron, 130-40
 Evolution, 87 90, 97
 Expressivity, 80
 Eye-colour, 84-7, 150

 Factors (see Genes)
 F generation, 10
 F₁ generation, 10
 Finney, 128
 First filial generation, 10
 First parental generation, 10
 Fish, 81
 Fisher, 2, 53-8, 66-7, 72, 82, 88-8,
 99-100 102, 117 119, 120
 Fertilization, 97
 Food allergy, 86
 Food, 87 82, 84, 89, 90, 99-100
 102
 Freemartin, 87
 Friedreich, 110
 Friedreich's Ataxia, 10, 78, 150

 Gamete, 142
 Gene-complex, 80-2, 84, 88-90
 Genes, 7, 144
 advantageous, 84
 controlling rate, 24, 94-7 122
 cumulative effects, 78-7
 disadvantageous, 82-4
 effects of, 78-83
 frequencies of, 120-8
 identical effects, 78
 interaction, 77-8, 80-8
 lethal, 82
 modifying, 77-8
 multiple effects, 79-80, 120
 mutant, 84
 sex-linked, 80
 variability of effects, 78, 86
 Genotype, 80
 Germline, 86
 Glaucoma, 160
 Goldschmidt, 20, 80
 Goodrich, 2, 90
 Grunberg, 86
 Guinea-pig, 20-1, 88
 Gunther, 82, 78
Gynandromorphs, 80
Gypops, 107 117

Haemolysis, 86
Haemophilia, 80-8, 45, 151
 A, 45-4, 150
 mild, 42, 82
 mutation rate, 82-3, 72
 Hair pigment, 18-21, 22, 128, 150
 wavy etc., 181
 woolly 81, 181
 Haldane, 40, 60-1, 60, 82, 71-2,
 85-9, 92, 118
 Haploid, 142
 individuals, 80
 Hare-lip, 48, 150-1
 Hay fever, 86
 Height, human, 78
 Heredity bisexual, 67-8
 blending, 7 48-70, 78
 cytoplasmic, 86
 maternal, 67-8
 Mendelian, 66-72, 118
 multi-factorial, 76-8, 127
 nuclear, 86
 particulate, 7, 69-70, 100, 118
 proof of, 66
 unisexal, 67-8
Hermaphrodite, 24, 28
Heterochromia iridis, 81
Heterogametes sex, 24, 86
 Heterogeneity, 126
 Heterophily, 80
 Heterozygote, 7, 86

- Hagben, 97
 Haemagglutinin, 24
 Homocercariasis 26
 Homocystosis, 7 80
 Huntington's chorea, 16, 85-6, 127,
 127, 130
 Huxley 66, 103
 Hydris, 14, 72, 80-1
 Hypogastrium, 79

 Ichthyosis, 51, 150-1
 Icm, 112, 118
 Inbreeding, 126
 Independent assortment, 17-21
 Infection, 65-6, 124
 Insanity 127-8
 Intelligencia, 151-3
 Interference, 22, 145
 Interphase, 147
 Intoxication, 26
 Intestinal cells, 24
 Invasion, 80, 143

 Jacarilla, 150, 157
 Jews, 107, 117, 120

 Keratodermis, 120
 King Edward VII, 43
 Kowung, 51

 Laceration, 70-1
 Laurence-Moon-Biedl syndrome,
 72, 82, 87 120
 Legal proceedings, 114-16
 Leptocera, 145
 Levi, 43
 Lichen urticatus, 95
 Leibniz, 123
 Light sensation, 95
 Linkage (autosomal), 23-6, 116,
 124-30
 groups, 27, 29
 Lipidosis, 150
 Loom, 23

 Macula lutea, 151
 Malkova, 43
 Maternal age 23-8
 Maiber, 40, 43, 120, 125
 Meiosis, 2, 24, 144-8
 Mendel, 8
 Mendelian ratios, 11 12, 19-21,
 40-2, 44-6
 standard error, 12-
- Mendel's first law 2-17
 second law 17-31
 Mental deficiency 79-80, 86,
 127-8
 Metaphase, 142, 147-8
 Miles, 65, 96
 Microphthalma, 151
 Migrants, 94
 Mitosis, 141-4, 148
 Mohr 81
 Mongolian idiosy 93
 Moths, 100
 Muller 64-8
 Mutation, 27-66, 115-18
 advantageous, 90
 chromosomal, 58-61, 64
 control of, 70
 disadvantageous, 20, 58-60
 genes, 58, 64
 genes affecting, 65, 64
 induction of, 64-6, 76
 localized, 61
 rate, 61-2, 70, 72-3, 116
 and selection, 65, 72
 reversion, 61, 62, 66, 120
 reverse, 61, 64
 somatic, 61, 63

 Nasal stoma infection, 95, 150
 Neurofibromatosis, 120
 Night blindness, 120
 Normal distribution, 77
 Nucleoplasm, 141
 Nervous, 141
 Nystagmus, 151

 Obesity 79
 Oedema, angioneurotic, 94, 129
 Oguchi's disease, 20-1, 151
 Ophthalmia, 23
 Optic nerve atrophy 151
 Optimum frequency 24, 121
 Oiler disease, 129

 Pachyema, 145
 Paternity, 115-16
 P generation, 10
 P generation, 10
 Penetrance 24-7, 22-8
 Penrose 22, 72, 82, 122-3
 Phenological symptoms, 22, 120
 Phenotype, 60
 Phenylketonuria, 20, 122, 150
 Phenyl-thio-urea, 2 of seq., 101-2,
 120

Twin, 86, 123-4
Tympanic membrane, 151

Uterine, 86
Use and abuse, 70

Vaginary, 123
Variation, 126
 ectopic, 77
 ectopic, 90-8
 genital, 90
Viability, 80, 117-18

Waddington, 8, 86
Webbed toes, 81, 151
White, 141

White forelock, 82, 151
Wiener, 107, 109, 112, 118
Worms, 87

X-chromosome, 32, 36
Xanthoderma pigmentosa, 42, 51,
 84, 151
Xanthoderma, 51
X-ray, 64-6

Y-chromosome, 32, 36

Yersin, 87
Yggis, 7
Yggis, 148

- Philp, 49
 Physiology genetic, 96-8
 Pisabala, 88, 160
 Pituitary body, 98
 Platyrrhini, 81
 Pneumonia, 134
 Polydactyly 72, 86, 160
 Polymorphism, 89
 applications, 114-18
 balanced, 100-1, 117
 genetics, 114
 medical aspects, 116-18
 and sex, 101
 survival with, 117 18
 transient, 100, 117
 Polyploidy 89
 Popcorn, 78
 Porokeratosis, 160
 Porphyria, 180
 Position effect, 81
 Poultry 88
 Premature baldness, 82, 180
 Price, 109
 Prometaphase, 143-3, 147
 Prophase, 142, 145-8
 Protoplasm, 141
 Quantitative differences, 78-7
 methods, 119-28
 Queen Victoria, 43
 Rabbits, 112
 albino, 25-7 124-8
 chinchilla, 92
 Himalayan, 92
 rex, 78
 yellow fat, 25-7 96, 124-8
 Race, human, 87 91, 104-8, 117
 120
 Radiation, 64-8
 Radiology, 64-8
 Radicals, 64-8
 Recesives, 10, 12, 87, 136-8
 proportion of, 130-3
 Recombination, 8, 90
 classes, 26
 Rectal polyp, 160
 Reduction, 148
 Repulsion, 24, 26-7
 Resting stage, 141
 Retinal degeneration, 70
 Retinitis pigmentosa, 47-8, 80-1,
 78, 79, 160-1
 R, generation, 14
 Rhine monkey 114
 Roberts, 84-8
 Roberts, Fraser, R. 25-8, 182,
 184
 Saliva, antigen in, 104
 Sebaceous cysts, 160
 Second filial generation, 10
 Segregation, 2, 148
 Selection, 72, 82-90, 96-101
 human, 87-8, 97
 Semas, antigens in, 104
 Sex-controlled tabanias, 44,
 82-3, 96, 112
 Sex-determination, 22-8
 Sex-linked inheritance, 82
 Sex-linkage, 28-32, 46, 127
 and crossing-over 48-8, 80-1
 dominant, 48-8, 123-3
 gene-frequencies, 131-3
 partial, 48-81, 122-2
 reversal, 80
 total in X, 26-48
 Y 61 2
 Sex-ratio, 83-8
 and polymorphism, 101
 and selection, 88-8
 standard error, 124
 Sh, 123
 Short, 8, 80
 Spastic paraplegia, 60, 160-1
 Spindle, 142
 attachment, 142-8
 Spindle, 142
 Spindle foot, 161
 Standard error, 122-8
 of differences, 128
 Stem-body 144
 Sterilization, 187
 Synchysis, 13, 23, 20
 Syphilis, 90, 184
 Tailor, 85
 Taste test, 9 of sex, 181-8
 Taylor R, 107 100, 112, 114, 118
 Teeth, deciduous, 80
 enamel of, 160-1
 incisors absent, 48, 160-1
 supernumerary 181
 Telophase, 144, 147-8
 Temperature, 81-3
 Termination, 147
 Tetrads, 140
 Tetraploidy, 80
 Therman, 2
 Transfusion, 104-8, 112
 and pregnancy 114
 repeated, 114
 Translocation, 60
 Tri-hybrid ratio, 21
 Triploidy, 80
 Tuberculosis, 134

- Trina, 88, 123-4
Tylosis palmata, 181

 Urinaria, 88
 Use and abuse, 70

 Vagueness, 123
 Vacation, 123
 continuous, 71
 environmental, 80-8
 periodic, 91
 Viability, 80, 117-18

 Waddington, 2, 68
 Webbed toes, 61, 181
 White, 141

 White heron, 82, 181
 Wiesner, 107, 109, 112, 118
 Wortall, 87

X-chromosomes, 22, 28
Xanthoxanthus pigmentosus, 40, 51,
 86, 181
Xiphophorus, 81
 X-rays, 84-6

Y-chromosomes, 22, 28

 Zetes, 97
 Zygote, 7
 Zygote, 148